ANNALS OF INTERNAL MEDICINE

PUBLISHED MONTHLY BY

The American College of Physicians

VOL. 35 (O.S., Vol. XL) SEPTEMBER, 1951 NUMBER 3

CONTENTS

Subscription per annum, net postpaid, $10.00, United States, Canada, Mexico, Cuba, Canal Zone, Hawaii, Puerto Rico, Philippine Islands, Central and South American Countries, and Spain; $11.00, other countries.

Entered as Second Class Matter August 21, 1933, at the Post Office at Lancaster, Pa., under the Act of March 3, 1879. Acceptance for mailing at a special rate of postage provided for in the Act of February 28, 1925, embodied in paragraph (d-2), section 34.40, P. L. & R. of 1948, authorized October 7, 1936.

ANNALS OF INTERNAL MEDICINE

VOLUME 35 SEPTEMBER, 1951 NUMBER 3

CARDIAC SYMPTOMS *

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THE subject of symptomatology will always retain its importance in medicine because symptoms form the first contact between patient and doctor. It is the voice of nature, and when a patient complains he enters our world and we recognize a human need. For convenience I shall apply the term "symptom" to subjective sensations of which the patient complains. While everyone agrees on their value in approaching a diagnosis, symptoms have been moved to the background by current interest in signs and in scientific technic. But if we apportion too little time for eliciting symptoms, we shall suffer in our diagnosis. Besides, knowledge acquired by the art of listening and of questioning has value far beyond a lead towards the diagnosis. A doctor learns what kind of human being faces him, and what reaction he is making to his malady.

It is a good plan to take the medical history in chronologic order; this will make not only diagnosis but prognosis easier, and the march of the disease can thus be estimated. Too often a patient will waste time by telling *why* it began; but we shall persuade him to tell *what* began, what it was that he felt. In cardiovascular cases, one may save a little time by omitting the family history. It has little or no value for diagnosis and not much for prognosis. Such retrospective inquiries may make a gloomy introduction to what might be a cheering interview, and I never make them. The practicing physician must primarily diagnose and treat the sick, and when so engaged he may be excused from collecting evidence about heredity and consanguinity in disease.

First, let us exclude symptoms which are popularly thought to arise from the heart but seldom do. *Weakness,* or undue exhaustion, is a good example, scarcely mentioned by a patient even in heart failure, and denied altogether by the anginal patient. We are not tired in the evening because

* Presented at the Thirty-second Annual Session of the American College of Physicians, St. Louis, Mo., April 9, 1951.

the heart is tired but because the nervous system has felt the day. The neuropath is inordinately tired. When weakness predominates, we think mostly of blood diseases, diabetes, growths, infections, especially tubercle, and so on, but not of heart disease, unless, indeed, there is rheumatic carditis or bacterial endocarditis.

Dizziness, or vertigo, is a widespread complaint generally accompanied by others, but it does not arise from heart disease or hypertension nearly so often as is supposed both within the profession and without. If it is the leading symptom, we think first of aural vertigo, occasionally of intracranial disease, and often of psychoneurosis. The minor attacks of Stokes-Adams disease may be described by a patient as dizzy attacks, but in reality they are faintness.

I propose to confine my remarks to the two main cardiac symptoms, dyspnea and pain, and to omit palpitation and syncope, which are lesser cardiac symptoms.

Cardiac Dyspnea

In assessing *dyspnea* we take into account age, training, weight and fitness—and that includes fitness in nerve as well as in body. You are well aware that the anemic and the bronchitic, and many other sick persons, share with the cardiac this respiratory consciousness. Much has been written on estimating the functional efficiency of the heart, but nothing more to the point than Mackenzie's criterion, "the ease with which breathlessness is induced." A man finds himself becoming breathless on his accustomed walk to the station or to get his car.

In another category is dyspnea that is spontaneous, paroxysmal and unrelated to exertion. You will have seen it occasionally without any premonitory shortness of breath on exertion, and where it appears as a dreadful and unexpected heart attack in the middle of the night. These paroxysmal dyspneas arise from left ventricular failure consequent upon hypertension, aortic incompetence (especially syphilitic), aortic stenosis or cardiac infarction. Morphine by injection has a wonderful, almost specific effect, and it is an insult to the grievously sick to offer a meaner remedy.

Many of you here will remember tumbling into bed late at night completely exhausted by the heavy day of a conscientious intern or resident. Great days—yet it was during your sleep that some newly-admitted cardiac patient would be having his attack of nocturnal dyspnea. There are many gaps in our knowledge and this is one of them, namely, the nature and mechanism of the paroxysmal dyspneas. It seems to me that a progressive hospital might institute a night squad of half-a-dozen keen men, a task force or commando, who would sleep by day and come forth at midnight to carry out close research in the wards on these very attacks. They would use up-to-date methods and apparatus for physiologic and pharmacologic study, while bearing in mind that treatment and prevention of recurrence

must be the ultimate purpose of their mission on behalf of clinical science.

As a medical student I was impatient of the space in textbooks devoted to differential diagnosis, feeling that it was superfluous, even far-fetched. Practice has reversed in me that early attitude, and many years ago I started a card-index of some of my own mistakes in diagnosis which had been exposed by time or post mortem. Such records have served to strengthen a few opinions on diagnosis submitted to you this evening.

First, *pulmonary* disease has to be excluded. Acute bronchitis recurring in the subject of bronchitis and emphysema can produce a state very like that of congestive heart failure. In contrast, a bout of cough or orthopnea at night in patients over 50 without any bronchitic history may usher in a left ventricular failure. The winglike areas of hilar congestion are the characteristic sign on fluoroscopy. Chronic bronchitis may hide a slow pulmonary tuberculosis in the elderly. Cancer of the lung is not rarely the cause of an insistent day-and-night dyspnea, developing in recent weeks or months when there was never dyspnea before. It may be accompanied by an obstinate cough, which should not be lightly accepted as due to cigarette smoking. We should think early of a bronchial growth when the dyspnea precedes signs, including roentgen-ray signs.

Emphysema is a common source of error, and a high value is placed on symptoms in this diagnosis. Any mention of periods of asthma or bronchial spasm or wheezing in the history may be significant, and we remember that a persistent cough is not expected in heart disease unless there is failure. Steadily increasing dyspnea on exertion in chronic bronchitis or asthma is suggestive if cardiac signs are absent. Routine fluoroscopy may show an inflated chest with a small-looking heart and a prominent pulmonary artery with some right heart enlargement. Too often in the emphysematous an associated hypertension is discounted, though it may later prove to be the predominant partner in producing failure.

Mention should be made of the obstructive dyspneas, not forgetting substernal goiter. On a minor plane, a man may get used to a collar too tight for free breathing, or a woman may have missed the advertisement that "some girdles leave you beautiful but breathless."

Secondly, *blood diseases*, notably anemia, readily cause dyspnea on effort, and when there is also edema the resemblance to cardiac disease may be close. Inquiring deeper, we remember the hidden bleedings from duodenal ulcer or from hemorrhoids, and, deeper still, too often some malignant disease, perhaps secondary.

Thirdly, *obscure heart disease* is to be considered. Though coronary artery disease is easily implicated when pain is the symptom, it can also be a quiet but real source of dyspnea. While the heart is of normal size, or nearly so, the electrocardiogram may show a bundle-branch block telling of myocardial involvement, or may reveal an old and unsuspected infarct. We are considering elderly patients without hypertension or obvious valvular

disease who are too breathless. Have we missed aortic stenosis? We no longer expect the small pulse and pulse-pressure of the textbooks, but notice a systolic murmur at the apex, and another, often but not invariably louder, at the aortic area. Get the patient to bend well forward, really bend; with deep expiration your hand may feel the telltale thrill. After that you may like to find and watch by fluoroscopy the calcified valve in motion. The cause of the dyspnea, perhaps also of pain, lies there, and the electrocardiogram will be in keeping. In some of my cases, unexplained dyspnea on exertion proved to be premonitory of an abnormal rhythm, such as fibrillation or flutter; in others, dyspnea preceded by weeks or months an angina of effort or a cardiac infarction.

Fourth and lastly, *nervous or psychogenic* dyspnea may be overlooked, for it is not very common. There are two forms, the first a rapid respiration at rest, a nervous tachypnea, and it will be one of multiple symptoms; the other, and commoner, form is well named "sighing respiration," and it occurs in anxious patients, especially women. Here the patient complains of shortness of breath when she is tired or worried, at any time, not especially during exertion. There is a compulsion yet an inability to take a deep or satisfying breath, so the breathing is shallow and irregular, apart from the sigh. It is a good plan to get the patient to imitate the breathing of which she complains.

Cardiac Pain

Leaving dyspnea, I will now turn to *cardiac pain,* proposing to speak of it in two groups. The first is pain arising from the heart but not due to coronary artery disease. The second group is cardiac pain from coronary disease, i.e., angina pectoris.

The first group is cardiac pain that is not angina pectoris. Naturally it has a similar site and distribution proper to a heart and not another organ, but the inadequacy of blood supply is not here due to disease of the coronary arteries. Why should not the heart produce a symptom, pain, if it fails to receive healthy blood or sufficient blood during a special call upon it? It can—and in the absence of coronary disease.

There are excellent examples, of which the best known are the cardiac pains in anemia, in paroxysmal tachycardia, in congenital malformations and in rheumatic valvular disease. These patients are suffering from their primary disease, but it is complicated on occasion by a cardiac pain similar to but seldom identical with the pain of angina. You will observe that they are not subject to the principal event, namely, cardiac infarction. Indeed, the prognosis seems to be unaffected by the occurrence of pain in these conditions. It is a misuse of the term, and gratuitous, to speak of these patients as having angina pectoris because they happen to have some pain. When they die, it will be because of their primary disease. You will agree that in the few anemic cases where pain occurs, cure of the anemia ends the problem

of the pain for that person. ' If the stress of an excessive rate in paroxysmal tachycardia produces in a few individuals a cardiac pain while the paroxysm lasts, this does not force them into the clinical course of a coronary disease. With rheumatic valvular lesions it is uncommon, and the pain, though often severe and recurrent, is little related to exertion. This is a cardiac pain due to insufficient blood for an excessive load, and the outcome will be that of the original disease, probably congestive failure. These are all examples of cardiac pain as a symptom.

My second and far more important group is painful coronary disease, and that, I maintain, is angina pectoris. I confess to being tired of hearing and reading that angina pectoris is a symptom, not a disease, believing that the pain is a symptom, and that angina is the coronary disease which produces it. Clifford Allbutt defined a disease as no more than our concept and our name for a certain recurrent series of morbid events in many living bodies, and insisted that angina pectoris is such. Nature helps doctors by repeating herself so often, almost nominating diseases; but she will not provide perfect symmetry for our convenience. Since coronary thrombosis was clinically discovered, thanks to Herrick, and its close affinity to other phases of painful coronary disease became evident, I have never grasped how anyone can still regard it merely as a symptom. My chief, James Mackenzie, was not the sort of man to die of a symptom. He had angina on effort and at rest, coronary insufficiency and failure, myocardial ischemia, coronary occlusion with thrombosis and cardiac infarction—but he died of angina pectoris, and the necropsy he demanded gave the pathologic changes of that disease. Incidentally, bearing on good prognosis after cardiac infarction, Mackenzie and Thomas Lewis both lived and worked for 17 years after their original attack. You notice the multiple terms I used to stress the advantage of a single comprehensive and euphonious title for a disease which, from its historic associations, its clinical uniformity and its causal pathology, should remain angina pectoris.

There is another point. It may be a convenience to use the term angina for that on effort, the pedestrian form, and cardiac infarction for the graver phase. But painful coronary disease cannot be expressed clinically by those two varieties. Does a man with effort angina cease to have angina when he gets attacks at rest, or worse attacks from infarction, or those many intermediate forms now in process of being isolated? He is the same afflicted man, and he has one and the same disease in evolution, namely, angina pectoris.

You will pardon this long digression on nomenclature, and I must now speak of the clinical approach to these patients with pain.

There is the difficulty as to what patients consider a pain, for discomfort or tightness in the chest may not be disclosed at all. We ourselves find it hard to define pain, especially in the slighter degrees accepted as discomforts. Difficulties multiply if it is only one of many symptoms, for pain is the single

symptom of the typical anginal patient. You will agree that it is often helpful to interview a wife or other relative, separately whenever possible, to confirm or supplement the all-important history. Time is not wasted in this endeavor, especially as we may wish to enlist their help in the plan of treatment.

One should insist on getting back to the time when the patient was well or in his usual health. This not only gives us the duration, but uncovers the very beginning of the symptom in its simplicity. Probably that early story will give away the direct relation to exertion which is the invaluable early clue. It is so often forgotten when overshadowed by subsequent and more memorable events, like longer anginal attacks at rest, or cardiac infarction itself. The pain may be a pressure or a tightness or a weight, but it is never of a stabbing kind. A few speak of a constriction around the chest as an accompaniment.

"Precordial" is too vague a term in any description of the site of the pain, in fact no better than the patient's "pain over the heart." Preference has grown for sternal pain, as the sternum is easily the commonest site, or the pain is across the chest and includes the sternum. Another significant area is the left supramammary, often extending into the left arm. So important is the exact site that I insist that every patient draw with his index finger a ring around the area of pain, however small or however large—the hand is far too inexact as a pointer. Following an analysis of unusual cases, one finds that angina pectoris may begin in the left arm alone, or even in the right arm, or both arms, the chest not being affected till later, maybe months later. Occasionally the pain on exertion may start in the left breast itself, though rarely below it. It may for a time be solely between the scapulae. Extension to the lower jaw is not uncommon, and a sort of anginal toothache during exertion may be remarkably produced. Rarely, too, the upper jaw, the mouth or the back of the mouth or throat is mentioned. Pain can move along the sides of the neck to the mastoids or beyond, or from the sternum to the larynx as a choking or gripping feeling. It does not move downwards from the sternum, except, perhaps, after cardiac infarction, when the liver swells from heart failure. Salivation occasionally accompanies the pain. Let us note the significant fact that anginal pain on effort and that in cardiac infarction differ in degree and duration only, not in site or extension.

Now we come to the unique characteristic, the occasion or immediate cause of early anginal pain, namely, effort. It is quantitative and corresponds to the effort undertaken. As Heberden said, "They . . . are seized while they are walking (more especially if it be up-hill and soon after eating) with a painful and most disagreeable sensation in the breast . . . but the moment they stand still all this uneasiness vanishes" (Heberden, 1768). It is rare in medicine for any other pain in the chest to arise from effort and to be so restrictive and even arresting. These people are well, apart from

the pain; as one man told me, "I feel strong enough to uproot that tree—but I can't walk to it"!

It proves possible for some people early in their experience of it to "walk off" the pain. A golfer who gets pain at the first hole or two, after nursing his disability by restraint during that period, finds that he can complete the course without further pain. This is an interesting phenomenon which has been described as a "second wind" for pain, or, recently, as "first effort angina." One such man told me, "I can walk through the pain"; another said, "After walking two minutes I get the pain but on standing it vanishes, then I can carry on and even walk across Hyde Park without getting it." Clinically this first effort angina leads on to the invariable pain on effort, with the usual course and prognosis.

In the differential diagnosis of angina of effort, I would place left inframammary pain high on the list because of its frequency. It is a persistent and tiresome ache below the left breast, sometimes enlivened by stabs or grips. Not only is it in the wrong place for angina, it is at the wrong time, namely, after, not during, exertion; in fact, when the patient is fatigued. The next is surely "indigestion," for a majority of patients imagine that it is, and want it to be, indigestion. It is worth while explaining to a reasonable patient on what grounds you dissent, even before bringing up your electrocardiographic reserves. His pain arises from walking after food, not merely from taking food. On occasion one may hint that there are worse things than pain from the heart, and there are. Among my admitted blunders in diagnosis are cases of carcinoma of the stomach, and ulcer of the stomach and duodenum, and cancer of the lung with and without pericardial involvement. But, curiously, some may think, gall-stones are absent from my index of errors, and so is hiatus hernia, which has postural symptoms, if any. Of course these conditions may co-exist with angina.

Too much stress should not be placed on extension to the left arm, common though it is. It can also occur in left inframammary pain of long standing, in esophageal disease and hiatus hernia, in high pleural disease or pneumothorax, and in spinal disease. Nitroglycerin has only a minor place as a diagnostic agent, for we know the beneficial effect often claimed by those with pain of psychologic origin. Yet it may prove to be a nice confirmation of the diagnosis of angina.

Before concluding, I should like to put in a plea for the wider use of vasodilators in treatment. Avoidance of the exertion which induces pain is the best policy of the anginal patient, but if pain cannot thus be avoided, he should be fully introduced to and make friends with the vasodilators. Most patients prefer nitroglycerin to amyl nitrite, and we should never fail to warn them of the sudden flushing and beating in the head which may be felt; many have blamed their doctor for neglecting to tell them of these side-effects. I am sure we do not prescribe it freely enough. The patient should be told that if the pain on exertion does not quickly pass off, he should *chew*

a tablet, not merely place it under the tongue. Every patient should be told explicitly that it is harmless, out of the system in a few minutes, and that it does not lose its effect with extended use. One man was afraid to try one because his doctor had carelessly said "There's dynamite in them, so be careful"! The prudent patient may use several a day without adverse comment, and two or more tablets may be used at a time if need be.

The preventive use of nitroglycerine has not yet received wide enough application, for it is a practice both serviceable and safe. We may thus promulgate the knowledge that the danger to life is now seen to lie with cardiac infarction and not with individual attacks of angina on effort. If pain is expected from some essential or desirable act of exertion, a tablet may be taken just before it is undertaken. One patient said, "Now I chew one in the bathroom, and that enables me to bathe and towel myself without pain." Patients have told me that, by this means, sexual relations were again rendered possible for them. A man may chew one before going out of doors to find his car. A keen golfer may learn that a single tablet will enable him to get a painless start and to complete the round with pleasure. A woman may take one before leaving her seat in the movies to prevent the pain expected on reaching the open air. Once, however, I prescribed it before a speech was to be given—and later on, reading the speech, I regretted it!

It is incumbent upon doctors not merely to prescribe a remedy, but to see that the patient makes full use of it. The bareness of our means, our poverty of treatment, oblige us to use what we have to the very limit. This is a fine example of proper treatment of a symptom, the pain of angina pectoris—symptomatic treatment at its best.

CLINICAL AND LABORATORY OBSERVATIONS ON AUTOIMMUNE HEMOLYTIC DISEASE*

By LAWRENCE E. YOUNG, F.A.C.P., GERALD MILLER, M.D., *Rochester, New York,* and RICHARD M. CHRISTIAN, M.D., *Greenwood, South Carolina*

THE term "acquired hemolytic anemia" has in the past been rather loosely applied to a heterogeneous group of hemolytic processes, but there has been a growing tendency to consider separately cases in which the patients have developed antibodies reacting with their own red corpuscles. Since our understanding of the autoimmune group of hemolytic disorders has grown rapidly during the past five years, it is appropriate that some of the recently accumulated information be analyzed at this time from the viewpoint of the internist.

This can best be done by considering autoimmune hemolytic disease with respect to: (1) serologic findings and pitfalls; (2) clinical course; (3) hematologic abnormalities, and (4) response to therapy.

The origin of the antibodies reacting with the patient's own red cells is a mystery. Autoantibodies develop independently in the majority of cases but may be encountered in patients suffering from any of a number of diseases, especially leukemia, the lymphomas, carcinomatosis, Boeck's sarcoid, tuberculosis and lupus erythematosus. The hemolytic process associated with autoantibodies may at times be the first clinical manifestation of these disorders. Serologic findings and abnormalities of the red cells in idiopathic cases are indistinguishable from those encountered in so-called "symptomatic" cases in which the hemolytic process accompanies another malady.[1, 2, 3] It is therefore appropriate to consider as a group all cases of hemolytic disease associated with autoantibodies having certain characteristics.†

SEROLOGIC FINDINGS AND PITFALLS

Since the presence of autoantibody active at body temperature is the *sine qua non* of the hemolytic disorder under discussion, methods of demonstra-

* Presented at the Thirty-second Annual Session of the American College of Physicians, St. Louis, Mo., April 11, 1951.

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The observations summarized in this paper were aided by a contract between the Office of Naval Research, Department of the Navy, and the University of Rochester (NR131-174), and were supported in part by the Hochstetter Fund.

† We have encountered cases of chronic hemolytic disease in which no autoantibodies could be demonstrated but in which the hematologic findings and clinical course appeared to be the same as in the cases described in this paper. The nature of the hemolytic agent or agents in such cases is obscure. It seems possible that autoantibodies may ultimately be demonstrated in the blood of some of these individuals if more sensitive serologic technics can be developed. It is also quite possible that non-immune mechanisms are responsible for the hemolytic process in certain instances.

ting the antibody attached to the patient's red cells and circulating in the plasma will be summarized before reviewing the clinical features of the disease.

Coombs, Mourant and Race [4] first showed that the presence of antibodies attached to red corpuscles could be demonstrated by mixing the washed red cells with antiglobulin rabbit serum.* Agglutination of the red cells presumably occurs because of reaction between erythrocyte-bound antibody globulin and antiglobulin in the serum prepared from rabbits immunized with normal human gamma globulin. The reaction may take place in the manner suggested by the simplified diagram shown in figure 1, which is a modification of a drawing published by van Loghem and associates.[5]

Boorman, Dodd and Loutit [6] in 1946 first applied the Coombs test in cases of acquired hemolytic anemia and found that the red cells of certain of these patients were readily agglutinated by antiglobulin serum. Experience

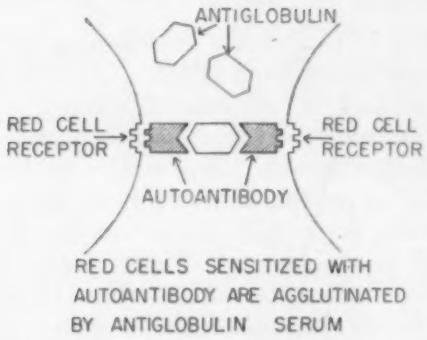

FIG. 1. Diagram suggesting manner in which red cells sensitized with autoantibody may be agglutinated by antiglobulin serum. Modified from figures of van Loghem et al.[5]

in many laboratories has since proved that the antiglobulin test has great value as a screening procedure in detecting erythrocyte-bound antibody in patients with the autoimmune type of hemolytic disease. Although the test is generally regarded as a relatively simple procedure, the results may be misleading if the importance of a few technical difficulties is not appreciated. Since the test has recently been accorded high standing in the clinical laboratory, it is essential that the clinician be aware of some of the major pitfalls in this procedure.

Causes of False-Negative Reactions: (1) There are variations in reactivity of different lots of rabbit serum with erythrocyte-bound antibodies of various specificities.[7] Hence, a negative result with a single serum, especially a weak serum, does not entirely exclude the diagnosis of autoimmune hemolytic disease. (2) Since some antiglobulin sera exhibit the prozone

* The principle of the antiglobulin reaction was described at an earlier date by Moreschi (Centralbl. f. Bakteriol. **46**: 49–51 and 456–460, 1908) who did not, however, distinguish between "complete" and "incomplete" antibodies.

phenomenon,[5, 7] cells tested with inadequately diluted serum may fail to agglutinate even though coated with antibody. (3) If the red cells are insufficiently washed before being mixed with antiglobulin serum, the mechanically adherent, nonspecific globulin may neutralize the antiglobulin antibodies, thus preventing their reaction with the specific erythrocyte-bound autoantibodies.

Causes of False-Positive Reactions: (1) If the rabbit serum employed is incompletely absorbed with normal human red cells before being used in actual tests, false-positive reactions may be obtained; that is, cells uncoated with antibody may be agglutinated by the serum. (2) Cold hemagglutinins present in the blood under various circumstances may at times sensitize red cells for the antiglobulin reaction even if the blood samples are kept at body temperature throughout preparation for the test.[7, 8] The Donath-Landsteiner type of antibody found in patients with paroxysmal cold hemoglobinuria also sensitizes red cells for the antiglobulin reaction.[9] Both cold agglutinins and

TABLE I

Methods of Demonstrating Autoantibody

Attached to the patient's erythrocytes

1. Agglutination of red cells by antiglobulin rabbit serum (Coombs test).
2. Agglutination of red cells when suspended in a mixture of albumin and normal human serum.
3. Elution of antibody from red cell stroma.

In the patient's serum

1. Agglutination of normal, compatible red cells suspended in albumin or normal human serum.
2. Agglutination of trypsinized normal, compatible red cells suspended in saline.
3. Sensitization of normal, compatible red cells for the antiglobulin reaction.

cold hemolysins may cause hemolytic anemia but should nevertheless be differentiated from the "warm" autoantibody, with which we are primarily concerned in this paper.

As indicated in table 1, coating of the patient's cells with autoantibody can also be inferred from agglutination of the cells when suspended in a mixture of albumin and normal human serum.[7, 10] The red cells may actually agglutinate in the patient's own plasma or in normal plasma, and this is easily seen by allowing oxalated blood to flow in a thin layer along the side of a glass container.[7] A more convincing procedure is that of elution of the antibody from the patient's red cell stroma by manipulation of pH and temperature of the cell-suspending medium.[7, 11] The eluted antibody is capable of sensitizing normal erythrocytes for the antiglobulin reaction, and it will also directly agglutinate normal red cells after trypsinization or suspension in albumin or normal human serum. Since this is the case, any of the antibody present in the patient's serum may also agglutinate normal compatible red cells suspended in albumin, normal serum or plasma, or trypsinized red cells suspended in saline, and it may sensitize normal erythrocytes for the anti-

globulin reaction.[7, 10-14] The antibody in the patient's serum becomes attached most readily to normal untreated red cells at a pH of 6.5 to 6.8, while pH has less effect on agglutination of trypsinized normal cells.[7, 14, 15]

Autoantibody which reacts with all types of human red cells must be carefully differentiated from specific, immune isoantibodies, such as anti-Rh, which are especially prone to develop after transfusion of patients with this disorder. In initial screening tests on patients suspected of having autoimmune hemolytic disease, we therefore prefer to demonstrate the antibody on the red cells and to postpone tests on the serum until the second round of investigation can be launched.

Cases Illustrating the Clinical Course of Autoimmune Hemolytic Disease

Figure 2 portrays the course of a typical idiopathic case of chronic autoimmune hemolytic disease. In this woman, who is now 72 years old, anemia gradually developed during the period between 1940 and 1945. At the time of splenectomy early in 1945, anemia was severe and was associated with persistent reticulocytosis and spherocytosis. The response to splenectomy was slow but ultimately quite satisfactory. In the summer of 1947, two and one-half years after operation, she had a hemolytic crisis associated again with brisk reticulocytosis, spherocytosis, increase in osmotic and mechanical fragility of the red cells, and a rise in serum bilirubin concentration. She gradually recovered from the anemia without treatment, and there has been no subsequent relapse.

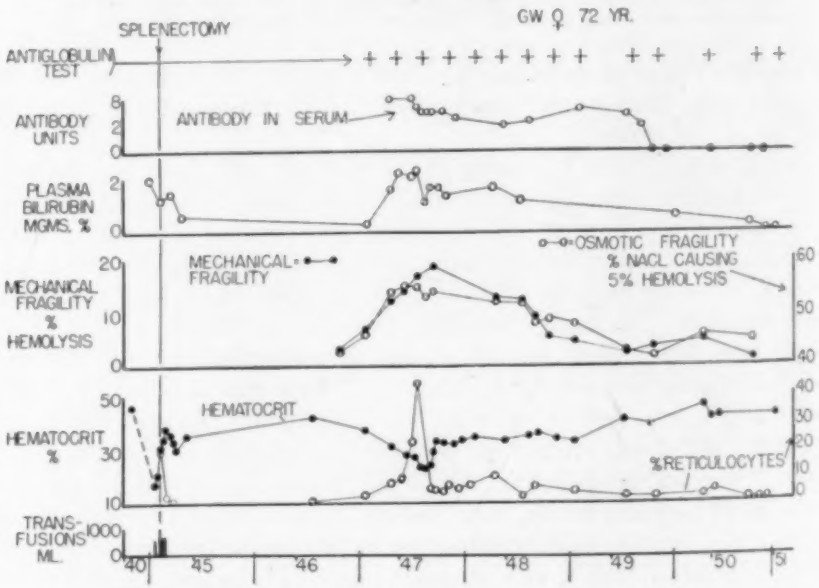

Fig. 2. Graph of principal laboratory data in case of G. W.

Since March, 1947, we have frequently tested the red cells of this patient with antiglobulin rabbit sera and at all times the cells have been strongly agglutinated by highly diluted serum. Results of the antiglobulin tests are recorded merely with + signs in figure 2 and subsequent graphs because quantitation of the Coombs reaction is difficult. The rate of red cell destruction in this patient and in most of the others investigated in our laboratory has been largely unrelated to the results of antiglobulin tests on the red cells (i.e., titrations of serially diluted rabbit sera against washed red cells from the respective patients). There has been some correlation, however, with the capacity of the patient's serum to agglutinate trypsinized normal red cells.

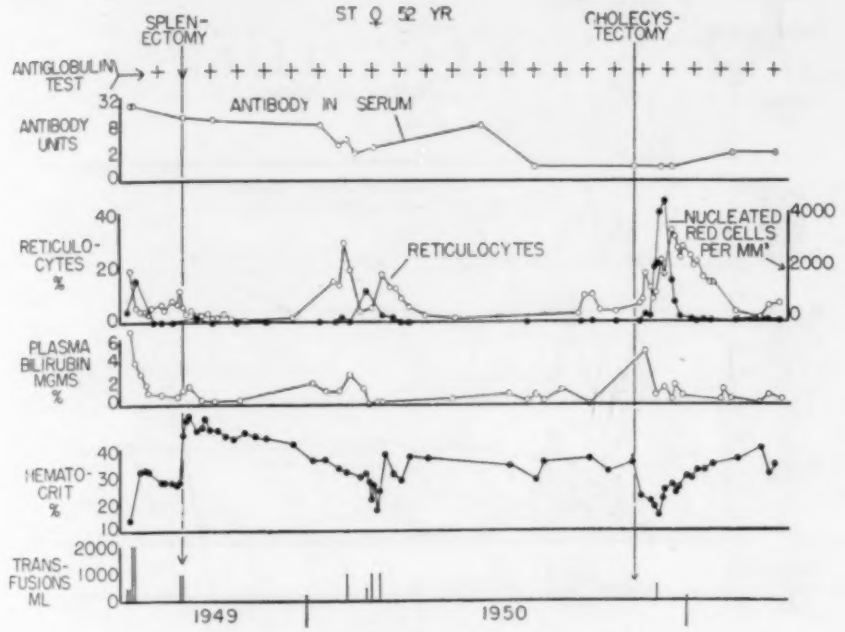

FIG. 3. Graph of laboratory data in case of S. T.

This case was chosen as an illustration because of the slow response to splenectomy, the relapse after splenectomy, and the spontaneous improvement after a hemolytic crisis. Spontaneous remissions of this sort should be kept in mind for comparison with results seen after administration of ACTH, radiation of lymph nodes, removal of accessory spleens and any other forms of therapy that may be used in treating this disease.

Figure 3 shows graphically the principal laboratory findings in a 52 year old woman who had hemolytic crises in August, 1949, February and March, 1950, and again in December, 1950. As in the previous case, relapses occurred after apparent response to splenectomy, and each crisis was

associated with spherocytosis, increased osmotic and mechanical fragility of the red cells,* bilirubinemia, reticulocytosis, normoblastosis and mild icterus. This patient, like many others with the same disease, had severe attacks of thrombophlebitis during each hemolytic episode. Recovery from the last relapse, which followed cholecystectomy, was rapid despite the fact that no therapy was given other than a single transfusion of 500 ml. of citrated blood. Throughout the period of observation of this patient, the red cells have invariably reacted strongly in antiglobulin tests while the titer of antibody in the serum has fluctuated significantly.

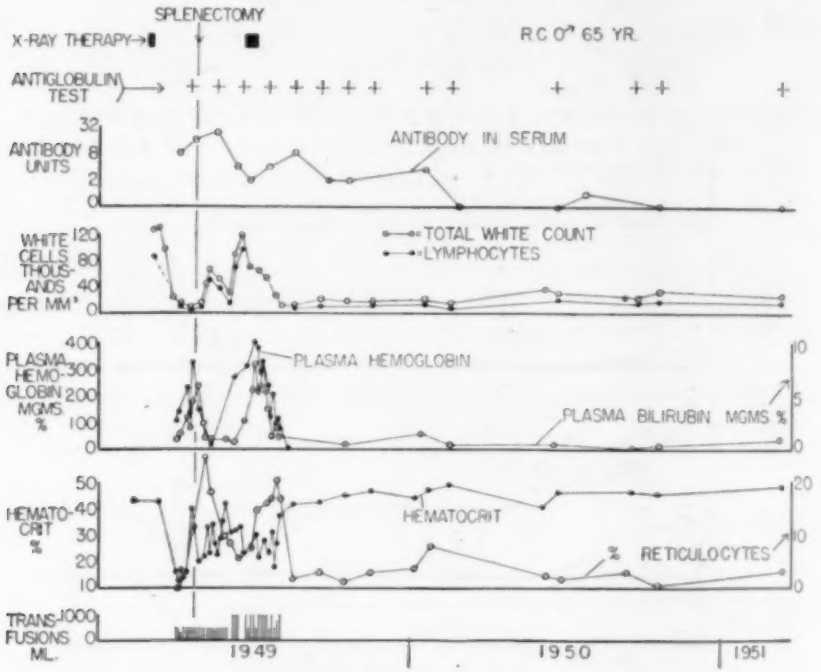

FIG. 4. Graph of laboratory data in case of R. C.

Figure 4 provides a summary of the laboratory data obtained in a 65 year old man with chronic lymphocytic leukemia and autoimmune hemolytic disease. Hemolytic crises in April and July, 1949, were associated with hemoglobinemia, methemalbuminemia, hemoglobinuria and jaundice. Since July, 1949, when the peripheral lymph nodes were irradiated, the nodes have not been palpable, the total white cell count has remained below 30,000 with preponderance of lymphocytes, and the hematocrit has remained within or near the normal range. This remarkable remission has been maintained

* Data revealing fluctuations in osmotic and mechanical fragility of the red cells and in fecal urobilinogen excretion in this case and in the following two cases will be presented in detail elsewhere.

over a period of 20 months without therapy of any sort and in spite of the fact that the red cells have continued to give positive antiglobulin reactions and that autoantibody has only recently disappeared from the serum.

Another illustrative case (figure 5) is that of a 54 year old woman who also has chronic lymphocytic leukemia complicated by autoimmune hemolytic disease. Evidence of leukemia was first recorded in 1944, and anemia developed for the first time late in 1949. A hemolytic crisis began in January, 1950, and during February, 1950, this patient destroyed both her own red cells and transfused red cells with great rapidity. She then received 100 mg. of ACTH daily for 10 days and 50 mg. daily for the next five days.

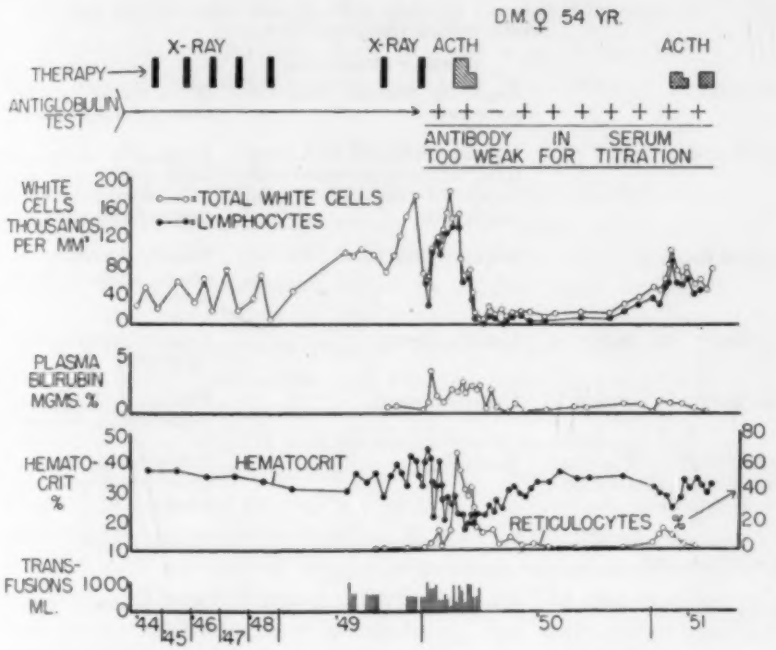

FIG. 5. Graph of laboratory data in case of D. M.

There was marked deceleration of red cell destruction after administration of ACTH, and the substantial remission in both leukemic and hemolytic processes was maintained for about nine months. Response to a second course of ACTH in February, 1951, was prompt though less dramatic than in the previous year. Antiglobulin tests on this patient's red cells became negative for a period of nine days during the first course of ACTH therapy, but have been positive at all other times. Although large amounts of cold precipitable globulin have been present in the serum during the past year, autoantibody has been demonstrated in the serum with difficulty. The spleen has never been palpable in this patient.

Hematologic Findings

Further comments on the hematologic findings in this disease can be made to advantage by drawing comparisons (table 2) with those in congenital hemolytic anemia or hereditary spherocytosis, the disorder most apt to cause confusion in differential diagnosis.

Spherocytosis and increased osmotic and mechanical fragility of the red cells are constant features of hereditary spherocytosis [16, 17] but are usually noted in the autoimmune disease only during periods of marked hemolytic activity.[3, 7]

Table II

Summary of Laboratory Findings in Hereditary Spherocytosis and Autoimmune Hemolytic Disease

	Hereditary Spherocytosis	Autoimmune Disease
Spherocytosis	Regularly present; slight in some cases	Often marked during crisis, absent during quiescence
Osmotic fragility	Usually increased with fresh cells; regularly increased with incubated cells even during quiescence	Irregularly increased with both fresh and incubated cells during crises, normal during quiescence
Mechanical fragility	Regularly increased	Usually increased during crises, normal during quiescence
Autoantibody on patient's red cells	Usually absent	Usually present even during quiescence
Autoantibody in patient's serum	Usually absent	Frequently present, especially during relapses
Shape and fragility of normal transfused red cells in patient's circulation	Normal	Sphering and increased fragility detectable in active cases
Rate of destruction of normal transfused red cells	Usually normal	Usually rapid
Trapping of red cells in spleen	Selective for patient's cells	Both patient's and donated cells
Thrombocytopenia (± leukopenia)	Usually absent	Frequently (?) present[22]
Similar laboratory findings in relatives	Usually present	Absent

Autoantibody is, by definition, present on the red cells and frequently in the serum of patients suffering from the latter disorder, while such antibody is usually absent in the inherited disease.[7, 16]

Since the so-called autoantibody is capable of reacting with human red cells of all types, normal transfused red cells show sphering and increased fragility and are rapidly destroyed after being placed in the circulation of patients with active autoimmune hemolytic disease.[1, 7, 18] Normal red cells transfused to patients with hereditary spherocytosis, on the other hand, usu-

ally undergo no demonstrable change in shape or fragility and their survival in such cases is usually normal.[11, 18-22]

The rôle of the spleen in the autoimmune disease has not been clearly defined. It may be an important site of antibody formation and it may also trap antibody-coated red cells.[2] In hereditary spherocytosis the patient's own red cells are selectively trapped in the spleen,[20, 21] probably because of their abnormal thickness, while in the autoimmune disorder donated red cells and the patient's own erythrocytes are affected indiscriminately by circulation through the spleen.[7]

Evans and associates [22] have found that thrombocytopenia occurs frequently, and leukopenia occasionally, in patients having red cells agglutinable by antiglobulin serum. Their observations suggest that platelets may be destroyed by antibody and that there may be a spectrum-like relationship between idiopathic thrombocytopenia and acquired hemolytic anemia.

Treatment

The chances of obtaining substantial benefit from splenectomy are great enough to justify recommending surgery in most cases, even though it is impossible to predict which patients will respond favorably.[7, 24] Remission of anemia often follows splenectomy, but some production of autoantibody continues and relapse may occur at any time, as in the typical cases already cited. It is therefore apparent that the spleen is not solely responsible for the manifestations of this disease, and that the term "hypersplenism" inadequately characterizes this chronic disorder.

Administration of ACTH and cortisone has been followed by marked deceleration of red cell destruction in some cases, but lengthy remissions like that obtained in our first patient are unusual.[2, 7, 25] Such therapy may be especially valuable in preparing acutely ill patients for splenectomy. Cortisone in tablet form has proved helpful in maintaining remissions in ambulatory patients.[2] Although the mode of action of ACTH and cortisone in this disease is poorly understood, it seems likely that their beneficial effect is mediated through reticuloendothelial and especially lymphatic tissues.[2]

Dameshek has reported an impressive remission in one case of acquired hemolytic anemia after administration of nitrogen mustard.[2] Experience with this form of therapy is too limited, however, for evaluation. Hemolytic anemia accompanying lymphocytic leukemia or lymphomas may be temporarily relieved after irradiation of lymph nodes. Other therapy aimed at an underlying disease may likewise be beneficial.

Transfusions of whole blood or red cells are necessary if anemia becomes severe, but excessive transfusions may accelerate the hemolytic process.[7] Cross-matching is often difficult because the autoantibody in the patient's serum may react with the red cells of all prospective donors and may be confused with specific isoantibodies, such as anti-Rh, which are prone to develop in these patients.

There is no rationale for use of iron compounds, liver extract, multiple vitamins and shotgun preparations in the treatment of this disease.

Recommendations

These remarks can best be concluded by making specific recommendations.

1. A high index of suspicion should be maintained for autoimmune hemolytic disease, especially in patients with refractory anemia, persistent reticulocytosis, hemoglobinemia, hemoglobinuria, mild icterus or splenomegaly.

2. The antiglobulin test deserves extensive use as a screening procedure in suspected cases, but the clinician should be aware of the fact that there are important technical difficulties in demonstrating and measuring autoantibody on the red cells and in the serum of affected patients.

3. Continuing search should be made for an underlying disorder, once the hemolytic process is demonstrated.

4. The natural course of autoimmune hemolytic disease should be kept in mind in evaluating response to any form of treatment that may be used.

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COBALAMIN (VITAMIN B_{12}) AND THE INTRINSIC FACTOR OF CASTLE *

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Vitamin B_{12}, originally isolated by Rickes and associates [1] in the United States and by Lester Smith [2] in England, is now known to be but one of a group of related compounds for which the generic term "cobalamin" has been proposed by its American discoverers. The several members of this group which have been isolated up to the present time are known as vitamins B_{12}, B_{12a}, B_{12b},† B_{12c} and B_{12d}.[3, 4, 5, 6] They have the same basic chemical structure, which is only partially understood but is known to contain one atom of cobalt and the ring structure 5:6, dimethylbenzimidazole in glycoside linkage with a molecule of ribose phosphorylated at C_2 or C_3.[7] Vitamin B_{12} itself contains a cyano group which is linked to the cobalt-containing moiety, and the term proposed for this compound is "cyano-cobalamin." [8] Vitamin B_{12b} lacks the cyano group and may be designated as hydroxycobalamin. All of the cobalamin analogues which have so far been obtained from natural sources possess the same type of biologic activity, although there are differences in the degree to which they promote the growth of test microörganisms. In the treatment of patients with Addisonian pernicious anemia, vitamins B_{12b}, B_{12c} and B_{12d} are apparently equally as effective, when given by parenteral injection, as vitamin B_{12} itself,[9, 10, 11, 12] although, as pointed out by Ungley,[10] appreciable differences in hemopoietic potency would have but slight effect on clinical response, and the detection of such differences would require a large number of clinical tests.

In the opinion of most investigators, cobalamin is the only agent present in significant amounts in concentrated liver extracts which is effective in the treatment of pernicious anemia. In crude extracts of liver, appreciable quantities of folic acid and possibly other as yet unidentified substances may be present. However, the experience of many observers who have been familiar with the evolution of therapy in pernicious anemia may be summarized in the statement of William P. Murphy: "The more highly concentrated and refined extracts insure the most satisfactory response. . . . There is no valid argument for the use of so-called 'crude' extracts in the treatment of pernicious anemia. . . ." [13]

* Presented at the Thirty-second Annual Session of the American College of Physicians, St. Louis, Mo., April 11, 1951.

From the Thomas Henry Simpson Memorial Institute for Medical Research, University of Michigan, Ann Arbor, Michigan, and the Wayne County General Hospital, Eloise, Michigan.

† Vitamin B_{12b}, isolated from liver and other sources, is apparently identical with vitamin B_{12a}, which was obtained by catalytic hydrogenation of crystalline vitamin B_{12}.

Since concentrated liver extract constitutes complete replacement therapy for pernicious anemia, and since the efficacy of such extracts appears to depend exclusively upon their content of cobalamin, it follows that solutions of crystalline cobalamin, or of cobalamin concentrates derived from sources other than liver, should be wholly effective as substitutes for liver extracts. Although this conclusion is not universally accepted, its correctness is supported by all published evidence. In our own experience with the use of cobalamin in the treatment of pernicious anemia, extending over three years, we have encountered no failure of response and no indication of relapse in patients receiving recommended maintenance therapy.

Numerous studies indicate that cobalamin is the dietary or extrinsic factor of Castle. The normal daily human requirement for cobalamin, supplied in the food, is unknown. From analyses of the cobalamin content of foods [14] it would appear that, unless meat, fish or eggs are eaten daily, the dietary intake of the vitamin is probably insignificant. Intestinal bacterial synthesis of cobalamin is a potential source of supply, but it is questionable if appreciable amounts of the vitamin are formed at levels of the intestinal tract where they may be absorbed.[15] Since patients with pernicious anemia, who may absorb no exogenous cobalamin, can be maintained in complete remission by the injection of the vitamin in a daily equivalent of 1 microgram,[16, 17, 18] it would appear that this quantity, absorbed from the intestinal contents, would adequately meet normal human requirements.

Nutritional macrocytic anemia may result from dietary lack of cobalamin (case 1), although this appears to be a less common etiologic factor in the development of such anemia than deficiency of folic acid. Chronic intestinal disorders may lead to impaired absorption of both cobalamin and folic acid and so result in macrocytic anemia (case 2). In Addisonian pernicious anemia, the primary defect appears to be lack of intrinsic factor of Castle which is required for the efficient utilization of cobalamin present in the gastrointestinal tract.

Except for the demonstration that the dietary extrinsic factor and the erythrocyte maturing factor of liver are identical and are, in fact, cobalamin, little progress has been made in the elucidation of the rôle played by the intrinsic factor since its existence was first postulated by Castle and his associates.[19, 20] The potentiating effect of normal gastric juice on orally administered cobalamin was first demonstrated by Berk and associates,[21] and their observations have been confirmed by others.[22, 23] Concentrated extract of gastric and intestinal mucosa of swine, which is hemopoietically inactive when given alone, produces optimal therapeutic responses when administered orally together with cobalamin.[24, 25, 26] These considerations apply to hydroxycobalamin (vitamin B_{12b}) as well as to cyanocobalamin (vitamin B_{12}). (See case 3.)

It has been shown by Ternberg and Eakin [27] that normal human gastric juice, saliva and extracts of the lining of the gastrointestinal tract of verte-

brates have the property of forming an unstable combination with cobalamin. In the complex so formed the vitamin fails to promote the growth of microorganisms which require exogenous cobalamin. The microbiologic activity of the vitamin may be restored by heating the complex. Ternberg and Eakin believe that the substance which combines with cobalamin is identical with intrinsic factor. However, the assumption appears to be unjustified that the capacity of biologic materials to form an unstable protein complex with cobalamin is necessarily a measure of the intrinsic factor activity of such substances. Nevertheless, in our experience there is a parallelism between the "binding" property and the intrinsic factor activity of human gastric juice and extracts of hog stomach and duodenum (table 1).

If intrinsic factor acts by combining with cobalamin and so rendering it unavailable to bacteria, its rôle might be explained as that of protecting the vitamin from utilization by organisms which, in the absence of an acid gastric secretion may inhabit the proximal portions of the small intestine. Abnormalities in the gastrointestinal flora of patients with pernicious anemia have been demonstrated by Davidson [28] and by Dick.[29] This concept gains some support from the observations of Lichtman, Ginsberg and Watson [30] that the administration of aureomycin to patients with pernicious anemia may enhance the activity of orally administered cobalamin. On the other hand, there are theoretic objections to this explanation, as well as clinical experimental observations which are not in accord with it. In the first place, if intrinsic factor functions as a protective mechanism when abnormal gastrointestinal conditions are present, then no physiologic rôle can be assigned to it in individuals without such abnormalities. On the experimental side, Girdwood [15] failed to demonstrate any consistent increase or decrease of cobalamin content of samples aspirated from the stomach and from progressively distal sites along the small intestine. Ungley [31] was unable to obtain a hemopoietic response in a patient with pernicious anemia to the oral administration of 80 micrograms of cobalamin given without intrinsic factor after partial sterilization of the intestine with aureomycin and other drugs. The patient subsequently responded to the same dose of cobalamin given with gastric juice.

If the protective theory were correct, the efficacy of intrinsic factor-cobalamin combinations in pernicious anemia should depend upon their microbiologic inactivity. It has previously been shown that a mixture of materials containing intrinsic and extrinsic factors after incubation is relatively heat stable as compared to the thermolability of the untreated source of intrinsic factor.[32, 33] We have recently reported that incubation of desiccated hog duodenal mucosa with cobalamin and subsequent heating of the mixture to 100° C. for five minutes result in a product with greater hemopoietic activity than when the mucosa was heated prior to incubation with cobalamin.[25] In a subsequent clinical experience (case 4), cobalamin was incubated with an extract of hog duodenal mucosa, thus rendering the vita-

min microbiologically inactive. The mixture was treated with a trypsin preparation at pH 8 for several hours at 37° C. and heated at 90–100° C. for 10 minutes to destroy any residual uncombined intrinsic factor. The resulting product was found to possess the microbiologic activity of its original content of cobalamin. When this preparation was given to a patient with pernicious anemia an excellent therapeutic response was obtained. Since the patient had previously failed to respond to orally administered cobalamin and since he obtained a good result from the preparation of cobalamin given in a mixture with heated, trypsin-digested duodenal mucosa,

TABLE I

Cobalamin Content, Cobalamin "Binding Capacity," and Relative Intrinsic Factor of Gastric and Duodenal Substances

Substance	Cobalamin Content Per Gm. of Material*	Amt. Required to "Bind" 1 μGm. of Cobalamin†		Amt.* Approx. Equiv. to 1 USP Oral Unit when Given with 5 μGm. of Cobalamin
		Aseptic Addition	Autoclaved 10 Min.	
Normal human gastric juice un-neutralized	"None"	200 c.c.	No "binding"	—
Gastric juice neutralized immediately after withdrawal	"None"	24 c.c.	No "binding"	75–100 c.c.
Hog gastric mucosa brand A	0.027 μgm.	"More than 100 mg."	—	Very low intrinsic factor activity
Whole hog duodenum	0.285 μgm.	"More than 100 mg."	—	10+ gm.
Hog duodenal mucosa	0.325 μgm.	95 mg.	—	2–4 gm.
Acid extract of whole hog duodenum	0.260 μgm.	22 mg.	120 mg.	1–2 gm.
Soluble fraction of non-dialyzable extract of hog duodenal mucosa	0.035 μgm.	12.5 mg.	60 mg.	0.75–1.5 gm.

* Dry weight ("lyophilized") except in case of gastric juice.
† Measured by inhibition of growth of *L. leichmannii*.

the inference may be drawn that intrinsic factor when in combination with cobalamin is relatively heat stable and resistant to trypsin digestion.

The foregoing observations also suggest that the absorbable form of cobalamin may be a complex containing one or more peptides. Although this concept may be partly correct, it would be unjustifiable to conclude that the interaction of cobalamin and intrinsic factor to form a peptide complex is a necessary prerequisite to the absorption of the vitamin. As shown by Ungley,[34] extremely large single oral doses of cobalamin (3,000 micrograms) are capable of producing significant responses in pernicious anemia, and since very little interaction with intrinsic factor may be presumed to occur in such

circumstances, it must be concluded that the vitamin is absorbed in unmodified form.

The clinical observations reported in this communication, to which reference has already been made, form a sequel to earlier publications on the hemopoietic effect of orally administered cobalamin and the intrinsic factor activity of various derivatives of hog stomach and duodenum.[24, 25] The methods of study have been previously described in these publications. In particular, all subjects received a diet lacking in animal protein except for one egg and one pint of milk daily. The time of administration of any medication was separated by at least two hours from that of ingestion of food.

The Effect of Orally Administered Cobalamin without Intrinsic Factor on Macrocytic Anemia Other than Addisonian Pernicious Anemia

Case 1 (chart 1): A 60 year old white male had macrocytic anemia considered to be on a nutritional basis. He gave a history of excessive alcoholic intake and dietary inadequacy. There was a 40 pound weight loss during the six months prior to admission. Liver function tests showed some abnormalities, but there was no clinical evidence of hepatic insufficiency, and the physical findings were not significant except for pallor and evidence of weight loss. Gastric analysis revealed the presence of free hydrochloric acid after histamine stimulation. Marrow aspiration revealed pernicious anemia type rubricytosis (megaloblastosis). Because of extreme weakness a blood transfusion of 500 c.c. was given; the post-transfusion erythrocyte count was 1,200,000 per cu. mm.; hemoglobin, 4.7 gm. per 100 c.c.; hematocrit, 15 per cent. Cyanocobalamin (vitamin B_{12}), 5 micrograms, and desiccated duodenal mucosa, 1.8 gm. were

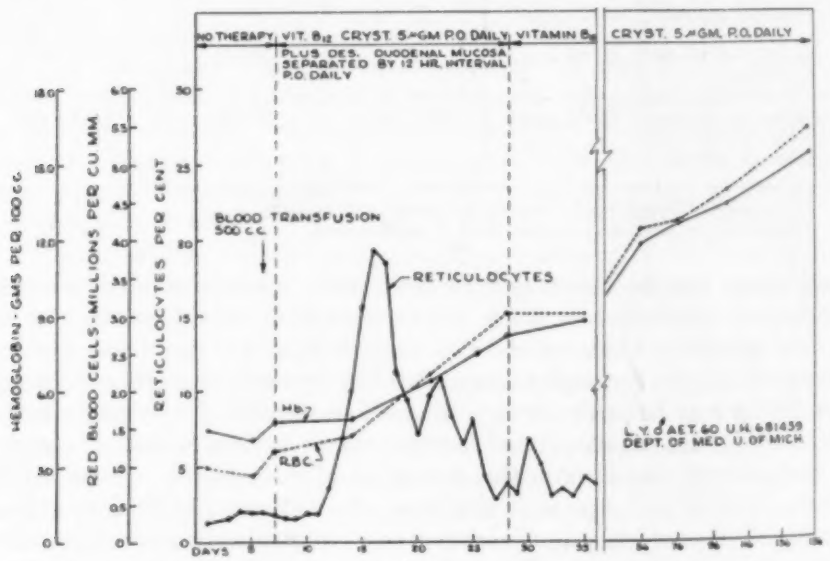

Chart 1. Nutritional macrocytic anemia treated with vitamin B_{12} orally.

given by mouth daily, but the administration of the two medications was separated by a 12 hour interval. A reticulocyte peak of 19.3 per cent was observed on the ninth day of treatment, and the erythrocyte count increased to 3,000,000 after 21 days of therapy. Subsequently, desiccated duodenal mucosa was discontinued and the erythrocytic values progressed to normal levels while the patient was receiving cyanocobalamin, 5 micrograms daily, without other medication.

Case 2 (chart 2): A 55 year old white woman had macrocytic anemia which was attributed to intestinal dysfunction and inadequate diet. Following irradiation therapy for carcinoma of the cervix 19 years earlier, she developed repeated intestinal obstruction, necessitating partial resection of the small and large bowel and ileotransverse colostomy. For three years prior to admission she had had severe diarrhea, which progressed until she was having 20 to 30 liquid stools per day. Because of the diarrhea she had reduced her food consumption and was subsisting chiefly on bread, cereals and tea. Free hydrochloric acid was obtained in the gastric secretions. Bone

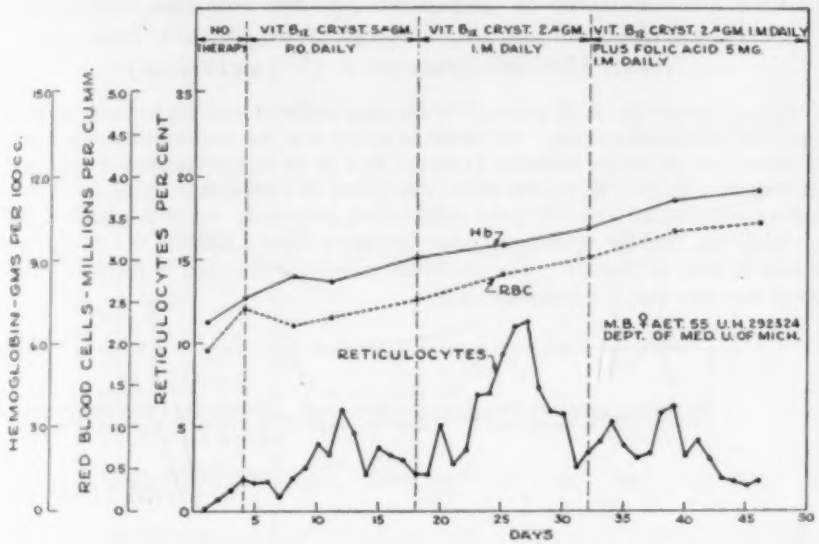

CHART 2. Nutritional macrocytic anemia treated with vitamin B_{12} and folic acid.

marrow aspiration revealed pernicious anemia type rubricytosis (megaloblastosis). The erythrocyte count before treatment was 2,400,000 per cu. mm.; hemoglobin, 7.5 gm. per 100 c.c.; hematocrit, 24 per cent. A significant but slight response was observed during the oral administration of cyanocobalamin, 5 micrograms daily. A greater rise in reticulocytes and more rapid increase in erythrocytes occurred when cyanocobalamin, 2 micrograms daily by intramuscular injection, was substituted for the oral medication. A third reticulocyte response occurred when folic acid, 5 mg. intramuscularly daily, was given in addition to parenteral cyanocobalamin.

Comment: In case 1, a simple nutritional deficiency of cobalamin is believed to have been present. The patient responded satisfactorily to a daily oral dose of 5 micrograms of cyanocobalamin without the simultaneous administration of a source of intrinsic factor. Although it is quite possible, and indeed probable, that this patient would have responded to folic acid

therapy, it is of interest that fully normal hematologic values and complete clinical well-being were attained while he was receiving cobalamin without other medication. It should be pointed out, however, that after the initial period of dietary restriction there was improvement in the quality of his diet.

Case 2 represents a complicated picture of dietary inadequacy and defective intestinal absorption involving both cobalamin and folic acid. Although some response was secured from orally administered cyanocobalamin, a greater effect was obtained when the vitamin was given parenterally, and remarkable hematologic and clinical improvement occurred when folic acid was given intramuscularly in addition to cobalamin.

The Requirement of Intrinsic Factor for the Effective Utilization in Pernicious Anemia of Orally Administered Hydroxycobalamin (Vitamin B_{12b})

Case 3 (chart 3): A 78 year old white man suffered with an entirely characteristic case of pernicious anemia. He failed to respond to the oral administration without intrinsic factor of cyanocobalamin (vitamin B_{12}) or hydroxycobalamin (vitamin B_{12b}), 5 micrograms daily. When the latter was given in combination with desiccated hog duodenal mucosa, 2.7 gm. daily, the reticulocyte percentage reached a peak of 16.9 on the eighth day, and the erythrocyte count increased from 1,100,000 to 2,320,000 during the first 21 days of therapy. The additional cobalamin supplied in the duodenal preparation was less than 1 microgram daily.

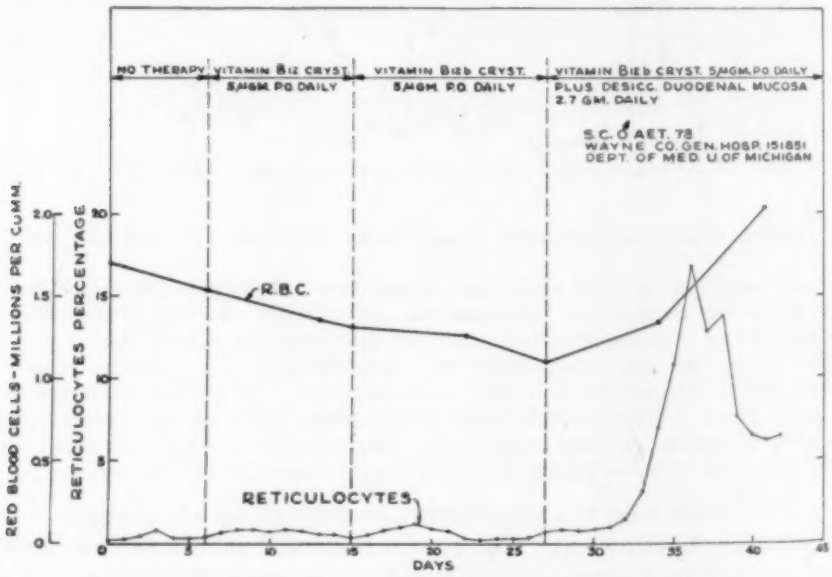

Chart 3. Response of a patient with pernicious anemia to the oral administration of vitamin B_{12b} given with desiccated hog duodenal mucosa after failure to respond to orally administered B_{12} and B_{12b} when given alone.

Comment: The observation that orally administered hydroxycobalamin (vitamin B_{12b}), like cyanocobalamin (vitamin B_{12}), is efficiently utilized by the pernicious anemia patient only when given together with a source of intrinsic factor was previously reported by one of us,[35] and is in agreement with the recent report of Schilling, Harris and Castle.[36]

The Effectiveness in Pernicious Anemia of Heated Trypsin Digest of an Intrinsic Factor-Cobalamin Complex

Case 4 (chart 4): A 58 year old white man with pernicious anemia was in severe relapse when admitted and required an immediate transfusion of 500 c.c. of blood. The post-transfusion erythrocyte count was 920,000 per cu. mm. when treatment was begun, in the form of cyanocobalamin, 5 micrograms daily, without a source of in-

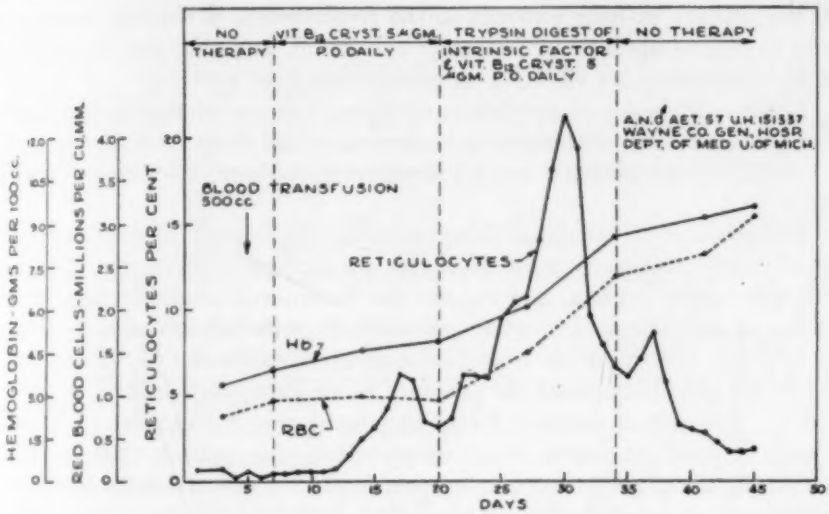

Chart 4. Pernicious anemia treated with trypsin digest of intrinsic factor and vitamin B_{12}.

trinsic factor. A maximal reticulocyte percentage of 6.1 was observed on the tenth day, but no increase in the erythrocyte count occurred during a two week period of therapy. In the second period the patient received daily a heated trypsin digest of an extract of duodenal mucosa which had been incubated with 5 micrograms of cyanocobalamin. The initial erythrocyte count was 920,000 per cu. mm. A reticulocyte peak of 20.9 per cent occurred on the tenth day of therapy. On the fourteenth day the erythrocyte count had increased to 2,330,000. At this point therapy was discontinued because of lack of material. During the ensuing 12 days, while no treatment was given, the erythrocyte count rose to 3,020,000.

Comment: The reason for employing the heated trypsin digested combination of intrinsic factor source and cobalamin, and the inferences drawn from the observations on this patient, have been discussed earlier in this communication. It may be pointed out that, although results obtained in a single clinical test do not justify far-reaching conclusions, nevertheless the

rate of erythrocyte increase observed in this patient is fully equal to the expected rise when one to two U.S.P. units of liver extract are given daily intramuscularly to patients with pernicious anemia.[37]

Summary and Conclusions

A number of chemically distinct forms of vitamin B_{12} have been isolated from biologic materials, and the generic term proposed for the entire group is cobalamin. Individual members have been designated as cyanocobalamin (vitamin B_{12}) and hydroxycobalamin (vitamin B_{12b}).

All of the cobalamin compounds which have so far been tested clinically possess the same type and apparently the same degree of hemopoietic activity.

The efficacy of liver extracts in the treatment of pernicious anemia appears to depend upon their content of cobalamin, and solutions of cobalamin given by injection are effective substitutes for liver extracts.

Dietary deficiency of cobalamin may result in severe macrocytic anemia. The condition may be completely corrected by the daily oral administration of crystalline cyanocobalamin, 5 micrograms, without a source of intrinsic factor.

Disturbance of intestinal function with diminished absorptive surface and dietary inadequacy may give rise to multiple deficiencies, associated with macrocytic anemia, and require the parenteral administration of both cobalamin and folic acid to achieve a satisfactory therapeutic result.

Efficient utilization of orally administered cobalamin by patients with pernicious anemia requires the presence of an exogenous source of intrinsic factor. The rôle of intrinsic factor in potentiating cobalamin is not understood. It does not appear to act by protecting the vitamin against destruction in the alimentary tract nor by preventing its utilization by bacteria inhabiting the stomach and small intestine.

There appears to be a parallelism between the intrinsic factor activity of gastric and duodenal preparations and their capacity to combine with cobalamin, thereby rendering the vitamin incapable of stimulating the growth of microörganisms which require it.

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THE USE OF CATION EXCHANGE RESINS IN CLINICAL SITUATIONS *

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Historical Aspects

The presence of substances in the soil capable of fixing cation constituents of fertilizers as a result of ion exchanging processes was first recognized by chemists more than 100 years ago.[1, 2] The current extensive industrial applications of the principle had their beginnings in water-softening processes,[3] during which positive charged electrolytes such as calcium or magnesium were removed. The advent of synthetic resins in 1935 [4] made possible for the first time the complete removal of both positive and negative charged ions, i.e., cations and anions from solutions in a wide variety of production processes. During the past five years, exploration of the possible therapeutic usefulness of these agents in clinical medicine has been stimulated by the demonstration that resins could be used to remove calcium from blood, measure total base, separate amino acids, concentrate radioactive isotopes, et cetera.[5–8] In 1946 anion exchange resins were first employed to heal peptic ulcers in patients following demonstration in vitro and in animals that they lowered the acidity of gastric contents without demonstrable toxic effects.[9–13] At about the same time, studies in animals were reported to indicate that ingestion of certain types of cation exchangers increased the fecal excretion of sodium and of potassium.[14] These findings logically suggested the possibility that resins might be used to evolve alternative and perhaps superior programs for the control of certain disorders of body sodium and potassium. This has indeed proved to be a fact. To date it has been established that the resins can be used to interfere with the absorption of ingested sodium and thereby lessen the need for rigid sodium restriction in patients with edema, hypertension or ascites; also, they can be employed to remove both endogenous and exogenous potassium. Whether this effect on potassium balances proves beneficial, inconsequential or undesirable will depend, as we shall see, upon the status of the body stores of this cation and upon the amount provided in the diet and the amounts removed in urine.

General Properties

Some description of the physical characteristics and the properties of the resins will facilitate the explanation of the above-cited effects and certain

* Presented at the Thirty-second Annual Session of the American College of Physicians, St. Louis, Mo., April 11, 1951.

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other concomitants of resin therapy. These agents are huge polymers of closely interlinked benzene rings, bearing certain chemical groupings which participate in the exchange process.[15-17] In the carboxylic type of resin, which to date has undergone the most extensive clinical testing, the component of this resin available for exchange with another cation is the hydrogen of the carboxyl or –COOH group. Prior to participation in the exchange process, this resin can be described as being in the acidic or hydrogen form. Following replacement of the hydrogen by another ion, such as potassium, it can properly be said to have been converted to the potassium form or, perhaps, more loosely, to the potassium cycle. Though highly insoluble and stable, these resins do swell in various solvents, and in water in particular. This property is based upon the fact that the hydrogen or sodium present in the carboxyl group ionizes in solutions, but remains in close proximity to the anion. The osmotic pressure inside the resin therefore at first exceeds that of the surrounding solvent, which moves into the interstices of the resin and produces some swelling. The resin can now participate in a cation exchange process. In general it can be stated that fundamental properties of the resin are such that, in dilute solutions and under identical circumstances at pH values above 3.5, divalent ions such as calcium will enter the resin in amounts greater than those characteristic for any of the univalent ions. On the other hand, of the univalent ions, more potassium than sodium will be found in the resin. This variable affinity of the resin for the various positively charged ions is dependent upon their atomic weight, their valence and the size of the ion, and can be modified by the degree of resin swelling, the nature of the solvent, the pH of the suspension, the concentrations of the various ions competing for a position in the resin,[15-17] and probably by a host of other as yet unidentified factors. The net results of the interplay of these factors upon the cation exchange process in the gastrointestinal tract are fairly predictable.

Effects of the Carboxylic Cation Exchangers on Serum and Stool Constituents

From the above considerations it is obvious that cation exchange resins possess certain potentialities for altering the composition of body fluids. Some of the less specific theoretic possibilities can be tabulated for confirmation or rejection in the light of available clinical, experimental and laboratory findings:

(1) Resins could interfere with appetite and satiety.

(2) These agents might influence bowel habit, producing constipation or diarrhea.

(3) They could hinder the function of the various gastrointestinal enzymes.

(4) Cation exchangers may conceivably prevent the absorption of digested carbohydrate, protein and lipid foodstuffs.

(5) The metabolism of intermediates might be modified during such therapy.

In addition to the above general speculations, it seems reasonable to extend the list into the realm of changes which might ensue subsequent to some of the more precisely defined biochemical effects of the resin:

(6) The absorption of elements released from the ingested resin, i.e., of the hydrogen, ammonium, sodium, potassium, calcium forms of the resin, might directly or indirectly modify serum concentrations and body balances of these constituents.

Insofar as our data are concerned, the answers to the first five of the above questions are quite clear: Ingestion of resin capsules can produce anorexia and even vomiting in some, but certainly not all, of our ill patients. Resin suspensions seem less distressing in this respect. Alterations in bowel habit have been minimal. We have not been able to detect any change in the overall exchanges of foodstuffs that provide materials and energy for bodily processes. This has been true even in our diabetic subjects. In this respect the results of our short-term studies are entirely in agreement with the animal experiments which have been reported in which larger dosage and more prolonged treatment schedules were used.[18-20] On the other hand, the

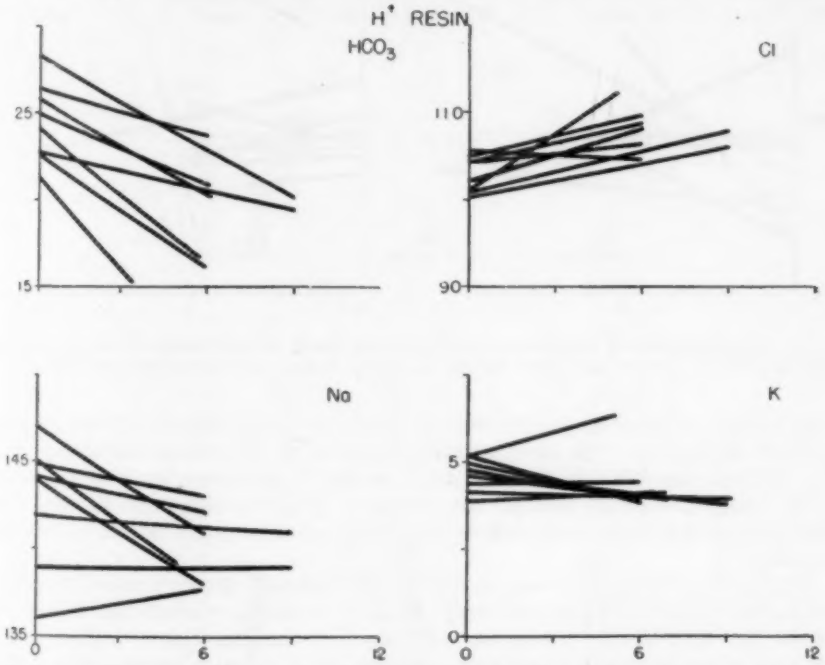

FIG. 1. Hydrogen cycle resin administered during eight periods produced fall in serum bicarbonate, rise in serum chloride and, generally, fall in potassium values. No consistent change in sodium concentration occurred.

bulk of our evidence does point to the occurrence of changes postulated in the sixth of the above-mentioned possibilities. Some of this evidence has been summarized graphically.

Figures 1 and 2 reveal that ingestion of approximately 40 gm. of either the hydrogen or the ammonium form of the carboxylic cation exchanger for three or more days by subjects maintained on a known intake of calories, electrolytes, and of nitrogen in a whole milk formula is associated with a decrease in serum CO_2 or bicarbonate content, and a variable rise in serum chloride concentration. These particular resins therefore induce changes which resemble those induced by acidifying diuretics.[21] The

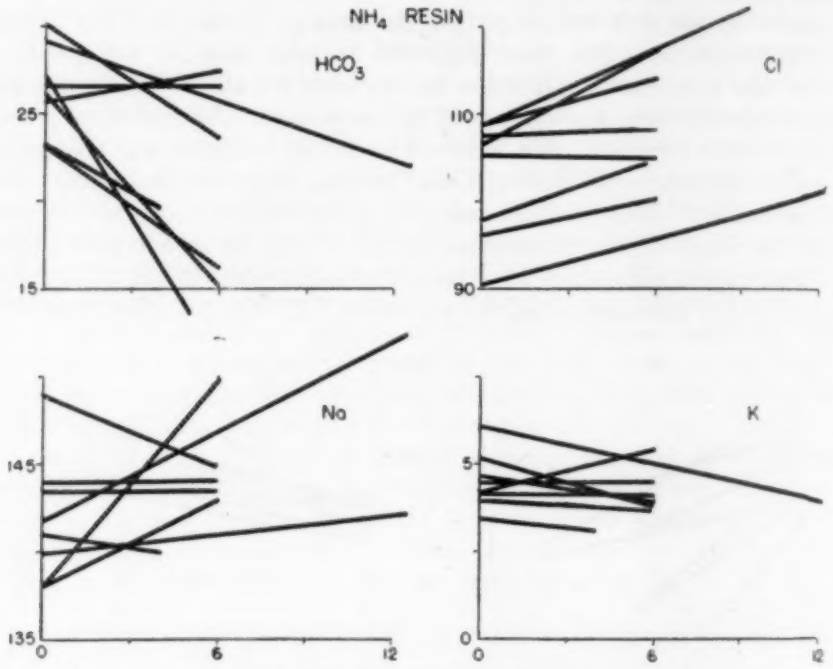

FIG. 2. Administration of the ammonium form of the resin resulted generally in acidosis and hyperchloremia, but no consistent change in serum sodium and potassium concentration.

serum sodium values undergo fluctuations which are no greater than those recorded in control observation. On the other hand, it should be emphasized that therapy with either of these two forms of the resin tends to reduce the serum levels of potassium. Finally, though the actual data are not presented, it can be added that in these same patients the serum phosphorus, calcium and fractionated proteins did not change significantly.

Figures 3 and 4 point to some of the intermediate steps through which the alterations in the serum have been mediated. Thus it is readily evident that exchangers in either the hydrogen or ammonium cycle augment the excretion of sodium and of potassium in stools without altering the nitrogen or the chloride output. The quantitative aspects of this observation merit some comment: Though the two cations were ingested in comparable amounts, the excretion of potassium in absolute terms was in-

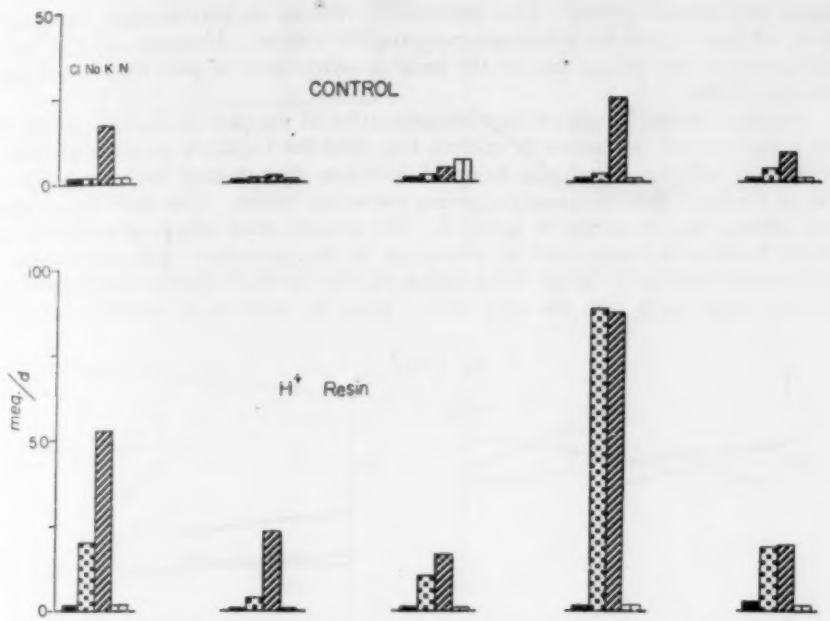

FIG. 3. In five patients, hydrogen form resin produced marked increase in stool sodium and potassium, but no change in chloride and nitrogen. The fourth patient received additional oral sodium.

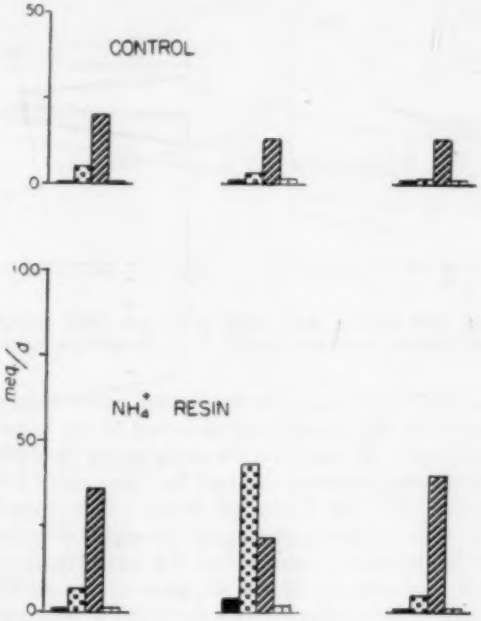

FIG. 4. Ammonium form of the resin augmented excretion of sodium and potassium in stool without change in chloride or nitrogen.

creased to a greater extent. This presumably reflects, in part at least, the greater affinity of these resins for potassium compared to sodium. However, another factor contributing to this finding may be the usual preponderance of potassium over sodium in normal stools.

Figures 5, 6 and 7 indicate that administration of the same exchanger precharged with either sodium, potassium or calcium ions does not regularly result in hyperchloremia or in acidosis. It should be noted, however, that therapy with the potassium form of the resin usually raised the serum potassium values. The stool data in these same patients are presented in figure 8. The greater stool output of sodium in the sodium form resin studies and of potassium in the potassium cycle experiments is readily understandable. Some of the cation ingested in the respective exchangers was excreted on or along with the resin itself. Even so, evidence is available indicating

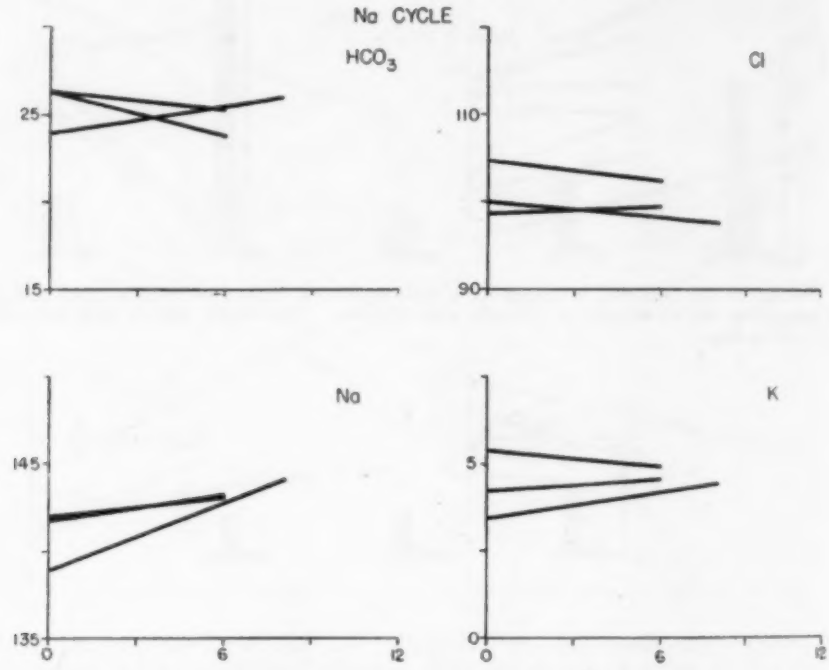

FIG. 5. During therapy with sodium cycle resin, there was little change in serum bicarbonate, chloride or potassium concentrations. A slight change in sodium occurred.

that during an intake of the exchanger in the sodium cycle, stool potassium increases and that the counterpart of this finding was observed in the experiment with the potassium form of the polymer. Finally, the one study of the stool effects of the calcium-charged resin presented here points to the fact that this agent exerts little influence, if any, on the sodium and potassium content of stools. This is not unexpected, in view of the greater predilection of these exchangers for divalent cations. This has been confirmed in supplementary studies, and serves the additional purpose of illustrating that any changes in the consistency or specific mass of the stools which might have been induced by these particular agents cannot account for their individual and characteristic effects.

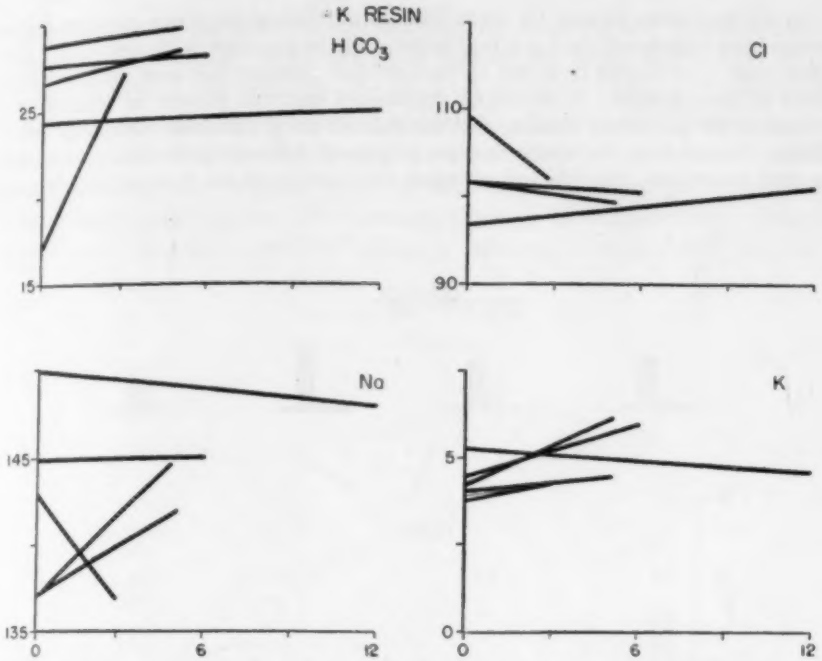

FIG. 6. The most important fact to be noted during administration of the potassium cycle resin is the rise in serum potassium concentration in four of the five patients studied.

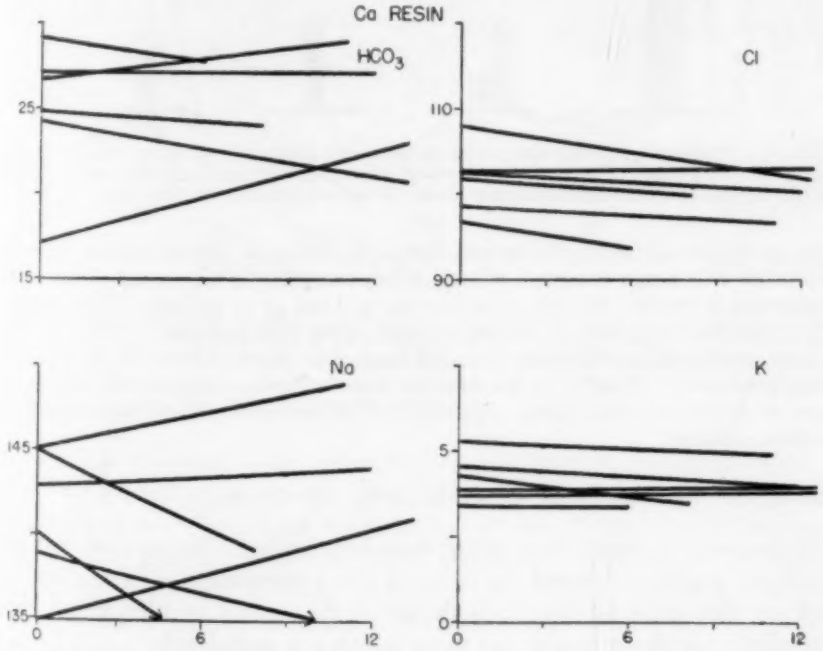

FIG. 7. Therapy with resin in the calcium form produced no change of serum chloride and potassium concentrations and no consistent changes in sodium and bicarbonate values.

In the final three figures (9, 10 and 11), a number of the resins alone or in combination have been tested during a protracted study in a patient with nephrosis. Compliance with or deviation from the above-described patterns has been indicated in the legends to these graphs. It should be emphasized that this patient, in contrast to all of those in the preceding studies, was maintained on a milk diet essentially free of sodium. Nonetheless, the serum changes in general followed previously noted trends. The stool potassium, chloride and nitrogen data confirmed the observations described

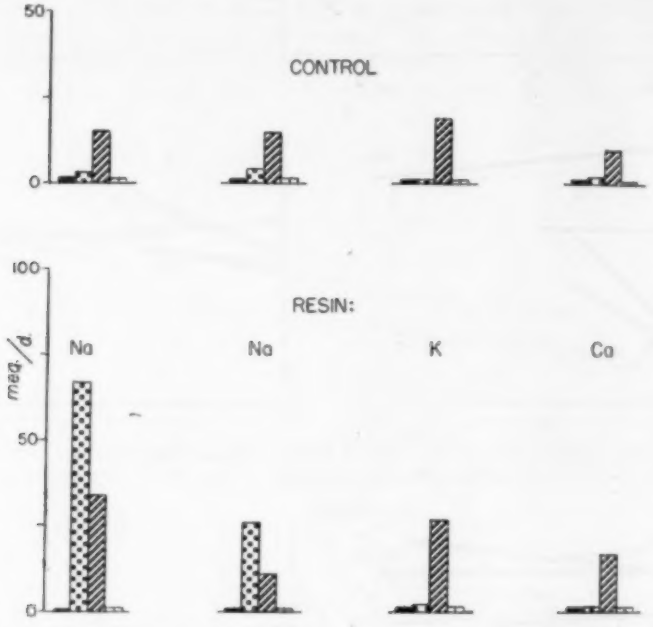

FIG. 8. Potassium and calcium forms of the resin produced no major change in stool electrolytes or nitrogen. The increase in sodium excretion with administration of the sodium form can be attributed to the augmented intake of sodium attached to the resin.

in the earlier studies with the various forms of the resin. Stool sodium, however, increased to only a minor degree, if at all, when compared to the results of the earlier investigation conducted on milk regimens unrestricted as to sodium. This points to the fact that the resins tend to remove ingested rather than endogenous sodium. This has been confirmed in additional extended studies in other children ill with the nephrotic syndrome.[2] Finally, to prepare the way for certain statements made in the section which follow, experiments with mixtures of the hydrogen and potassium forms have been included.

THE NET EFFECTS OF RESIN THERAPY

Unfortunately, description of the complete balance data on even this portion of our studies is beyond the scope of this presentation. Generalizations based on this material may nonetheless prove useful in identifying those resin effects which are useful and those which are undesirable.

First, it seems reasonable to suggest that the acidosis and hyperchloremia which accompany therapy with the hydrogen or the ammonium form of the resin may facilitate the delivery of edema in patients, exerting effects comparable to those seen with acidifying diuretics. Obviously this change may prove undesirable if it reaches proportions sufficient to produce an uncompensated acidosis or overbreathing. It can be avoided by judicious selection of resins in other cycles, administered alone or in combination. Second, it seems clear that the currently available carboxylic resins still possess a

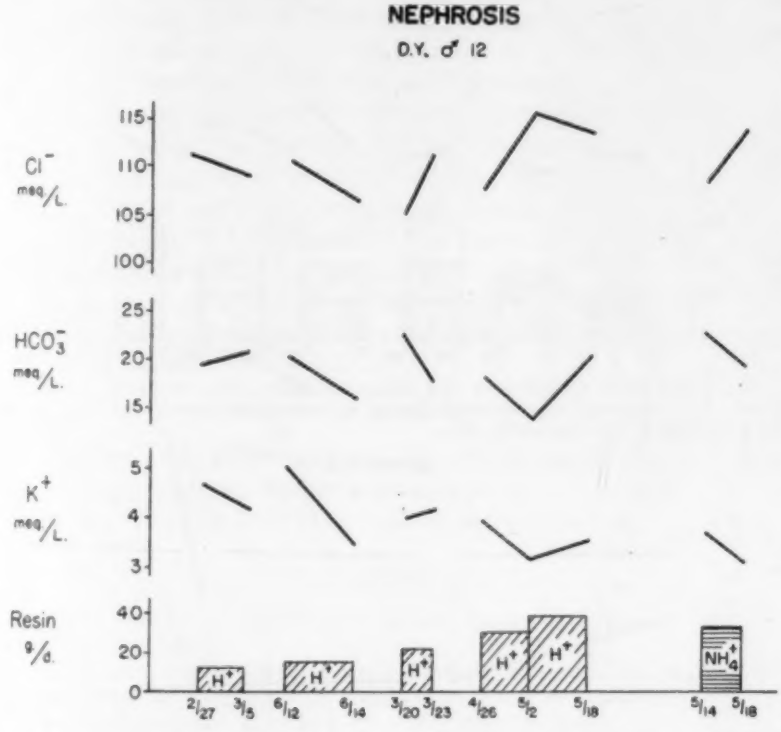

FIG. 9. Administration of cation exchange resin in the hydrogen form produced definite hyperchloremia and fall in bicarbonate when dosage exceeded 20 gm. daily. Similar amounts of the ammonium form of the resin produced comparable changes. Potassium concentration fell in all but one instance. There was a tendency for serum values to return toward control values as resin was given for longer periods.

relatively low efficiency with respect to their ability to deviate sodium to stools. As a matter of practical fact, they can at present be categorized only as adjuvants. Use of these agents will permit a somewhat more liberal intake of sodium in patients who must eschew this element. One cannot expect them, at present at least, to replace the truly sodium-free diet, nor can they be used to remove excessive body stores of sodium via the gastrointestinal route. Third, it should at no point be forgotten that these ex-

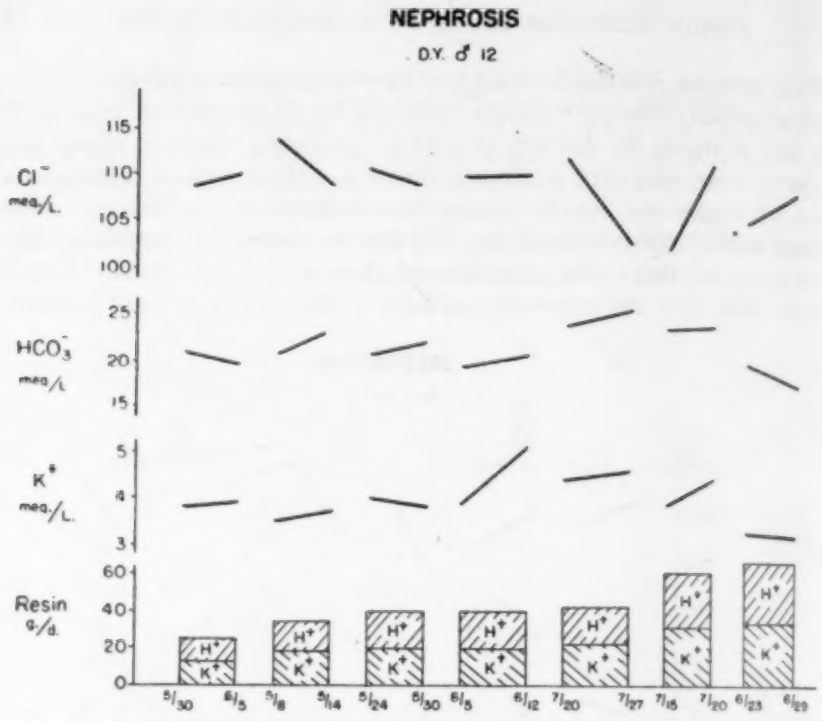

FIG. 10. Equal parts of hydrogen and potassium form resin, in dosage ranging from 24 to 66 gm. daily, produced no consistent change in serum concentration of chloride, bicarbonate or potassium in this nephrotic child.

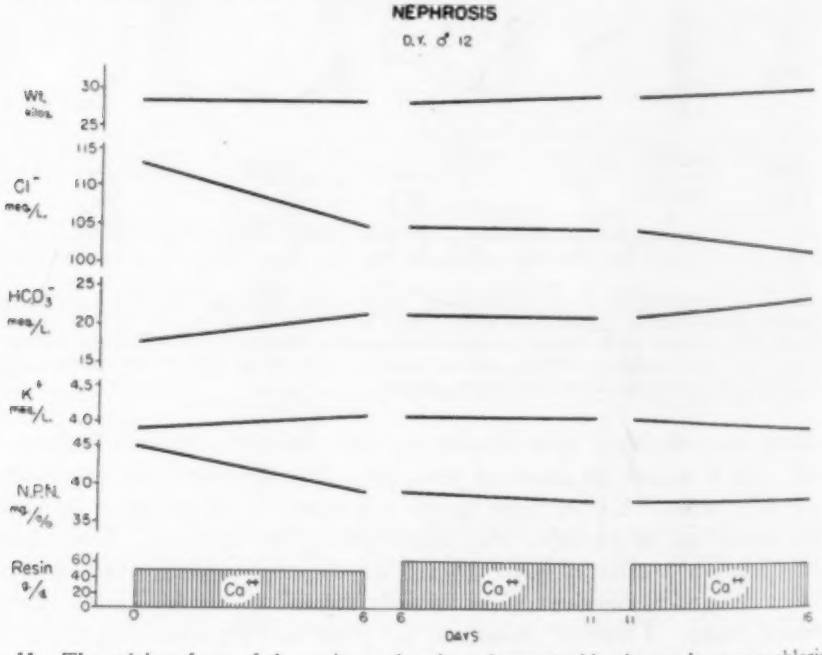

FIG. 11. The calcium form of the resin produced no demonstrable change in serum chloride, bicarbonate or potassium, even though doses as large as 60 gm. daily were given.

changers can very quickly and profoundly influence the exchanges of potassium. In all of the types tested, save for the calcium form, stool output of potassium rose significantly. It certainly cannot be denied that in some patients with potassium intoxication,[22 to 24] this effect could by itself prolong or permit survival. On the other hand, evidence is constantly being accumulated indicating that potassium deficits, irrespective of their mode of origin, can produce electrocardiographic changes, skeletal and cardiac muscle necrosis, and altered muscular function with paralysis or camouflage of hypocalcemia. Mortality data point also to the fact that these changes are of vital significance in the survival of ill patients.[25 to 30] Once again, therefore, a new therapeutic agent can be classified as a two-edged sword. Unfortunately, no convincing data have been presented as yet to suggest that the use of mixtures of resin forms obviates the need for careful observation of patients receiving this therapy, and for reliance upon clinical judgment and all available laboratory aids. The advent of exchange resin has provided the clinician with relatively simple means of influencing the composition and volume of body fluids.[31 to 37] There is every prospect that their efficiency and utility will be further extended. In the interim, it is extremely important to emphasize that enthusiasm must be tempered with judgment. The latter can only be reached following careful evaluation of the status of our individual patients.

Summary

The history, the properties and the clinical applications of synthetic cation exchange resins of the carboxylic type have been reviewed to assist the clinician in defining their potentialities and limitations.

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THE PLACE OF THE ELECTROCARDIOGRAM IN CARDIAC DIAGNOSIS *

By Francis F. Rosenbaum, M.D., F.A.C.P., *Milwaukee, Wisconsin*

Introduction

Nearly 50 years have passed since Einthoven introduced the string galvanometer. The instrument has become less cumbersome and less complex, and its clinical application has become increasingly simple. Electrocardiography is now so much a part of standard medical practice that many physicians and laymen feel that no general medical examination is complete without an electrocardiogram. It is inevitable, with such wide usage, that electrocardiograms or their interpretations come into the hands of men who are insufficiently grounded in fundamental considerations in the field of electrocardiography. In consequence, many patients are given diagnoses and prognoses which are unjustified and which may cause serious psychologic and economic suffering. The limitations of electrocardiography have been emphasized too little. The electrocardiogram rarely permits a diagnosis by itself; it is only one element of the entire picture. It is the correlation of the electrocardiogram with the other clinical and laboratory data which should be our aim. In this presentation I will try to indicate in some measure the place of electrocardiography in clinical cardiac diagnosis by illustrating some of the limitations and pitfalls in the method. By so doing, I may help to reduce the errors in electrocardiographic diagnosis which so beset us today.

Technical Quality of the Tracings

In order to be of real value, an electrocardiogram must be recorded properly. Artefacts may result from many causes, which need not be enumerated here. Probably the most common is improper preparation of the patient. Inadvertent interchange of lead wires is another error which, though quite obvious to the trained observer, seems often to go unrecognized. I have seen this error lead to incorrect diagnoses of myocardial infarction on several occasions. It is not my purpose to argue the merits of the various types of electrocardiographic instruments now available commercially, but it seems proper that each physician who undertakes to record or interpret electrocardiograms be familiar with the characteristics and possible limitations of his particular machine. If artefacts are present, they must be recognized and their origin understood. An electrocardiographic interpretation

* Presented at the Thirty-second Annual Session of the American College of Physicians, St. Louis, Mo., April 9, 1951.

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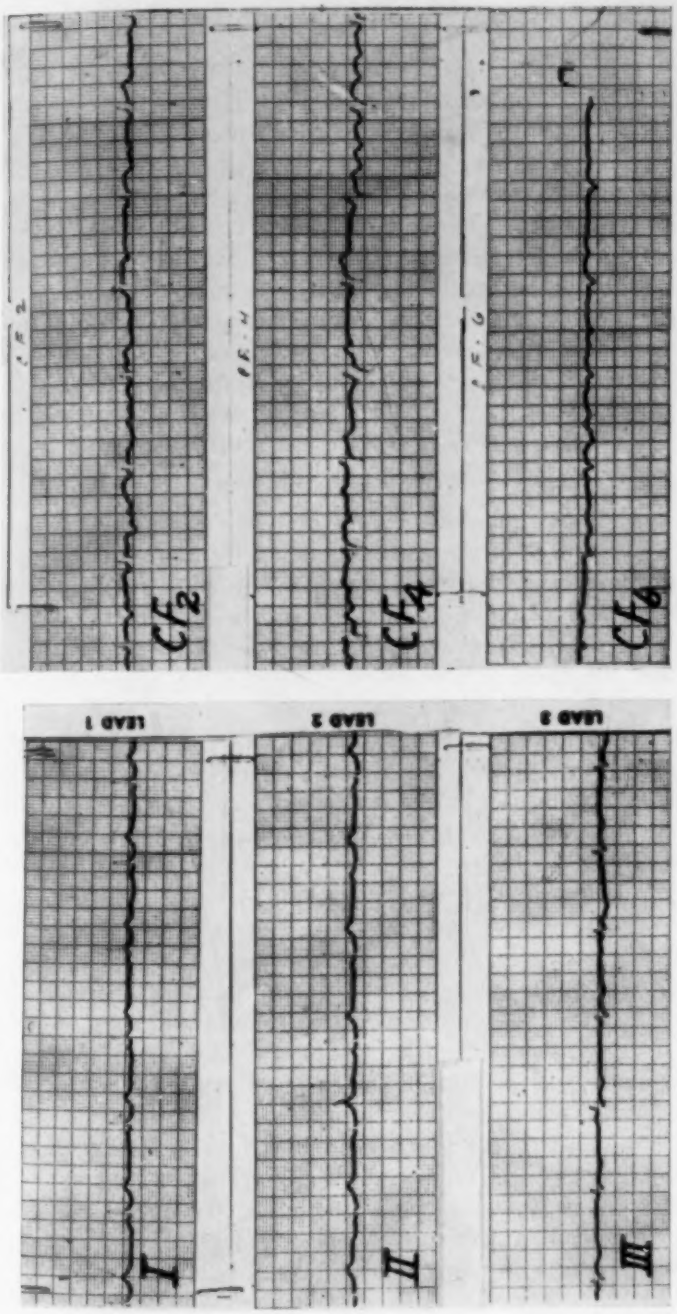

FIG. 1. Housewife, aged 40 years, who had pain beneath the left breast for several years prior to these electrocardiograms. The standard leads show no abnormalities. The precordial records, Leads CF_2, CF_4, and CF_6, are grossly distorted by artefacts. A diagnosis of "myocardial damage (strain) nonspecific" was made from this record. Complete clinical and electrocardiographic studies two weeks later showed no abnormalities, and the precordial electrocardiograms were entirely normal.

can be no better than the technical quality of the record from which it is made.

The electrocardiograms illustrated in figure 1 were taken on a 40 year old woman who had pain beneath the left breast. Numerous previous examinations and electrocardiograms had been normal. The records shown were recorded on December 16, 1950. It is obvious that the precordial electrocardiograms are valueless because of gross artefacts, yet the interpretation based upon this record was, "Myocardial damage (strain) nonspecific. Picture is not that of coronary disease." When seen in consultation two weeks later the patient was concerned because of the "strain of her heart." The complete cardiovascular and electrocardiographic study was normal. Because of electrocardiographic artefacts, this patient suffered a severe psychologic injury from which she may never recover despite repeated reassurances.

The Electrocardiogram in the Diagnosis of Disorders of the Cardiac Rhythm

The electrocardiogram has often been called the court of final appeal in the diagnosis of disorders of the cardiac rhythm. Certainly it is the most convenient and generally useful method available in clinical problems of this type. However, in order to interpret the arrhythmias recorded and to appreciate their significance from a therapeutic point of view, the physician must understand the basic pathologic physiology. To arrive at a correct diagnosis, careful measurement and analysis of the records are sometimes required and, at times, no small amount of imagination is also useful. Simple clinical physiologic experiments employing exercise, carotid sinus stimulation, or the administration of atropine or amyl nitrite may be required to alter the cardiac mechanism and add information which will permit a correct diagnosis. Additional electrocardiographic observations after trial doses of digitalis, quinidine, procaine or other drugs may be required. In problems of this general category we encounter many clear examples of the fruitful correlation of clinical and electrocardiographic study.

The tracings shown in figure 2 were recorded in a 60 year old man who had mitral insufficiency and infrequent paroxysms of rapid heart action. An attack began five and one-half hours before the initial records shown here. Because of the ventricular rate of 160 per minute and the bizarre outline of the QRS complexes, the patient was considered to have paroxysmal ventricular tachycardia. He was given quinidine sulfate, 1.6 gm. (gr. 24) orally and 0.2 gm. (gr. 3) intramuscularly in a period of six hours. When the patient was seen in consultation at the end of that time it was felt that the initial tracings represented auricular flutter with 2:1 atrioventricular block, and that the bizarre QRS complexes were due to aberrant ventricular responses or permanent intraventricular block. Additional electrocardiographic observations at this time showed greater widening of the QRS interval and brief runs of an idioventricular rhythm, both suggesting serious

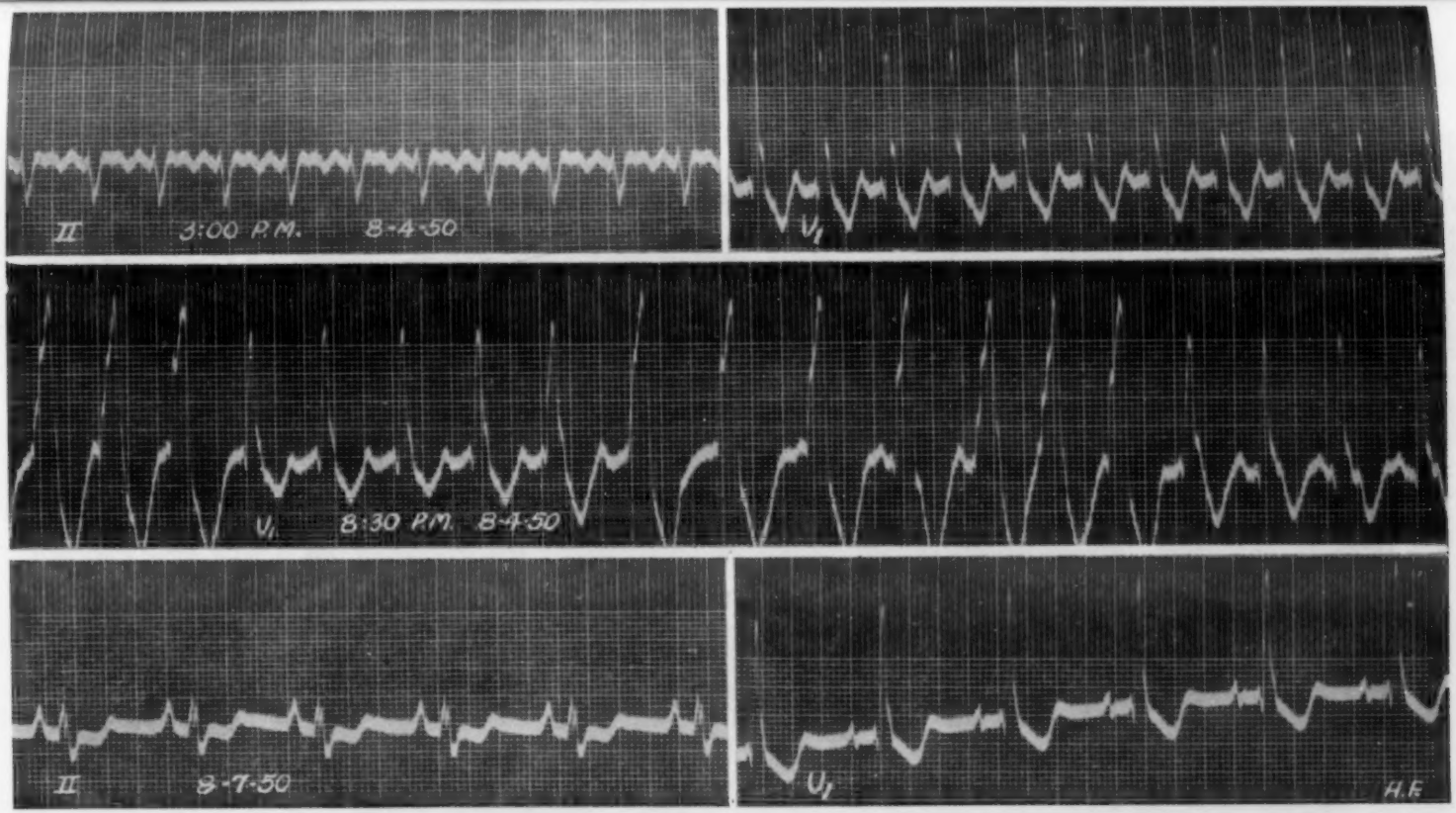

FIG. 2. Salesman, aged 60 years, with rheumatic heart disease. Paroxysmal rapid heart action began at 10:00 a.m. on August 4, 1950. Upper records—3:00 p.m.: auricular flutter with 2:1 A–V block and bizarre QRS complexes. Original impression was paroxysmal ventricular tachycardia. Middle records—8:30 p.m.: the QRS complexes have become wider and there are brief paroxysms of an idioventricular rhythm. Patient had received quinidine sulfate, 1.8 gm. (gr. 27) orally and intramuscularly. Lower record—August 7, 1950: Normal sinus rhythm is present. It is evident that the patient has permanent complete right bundle branch block.

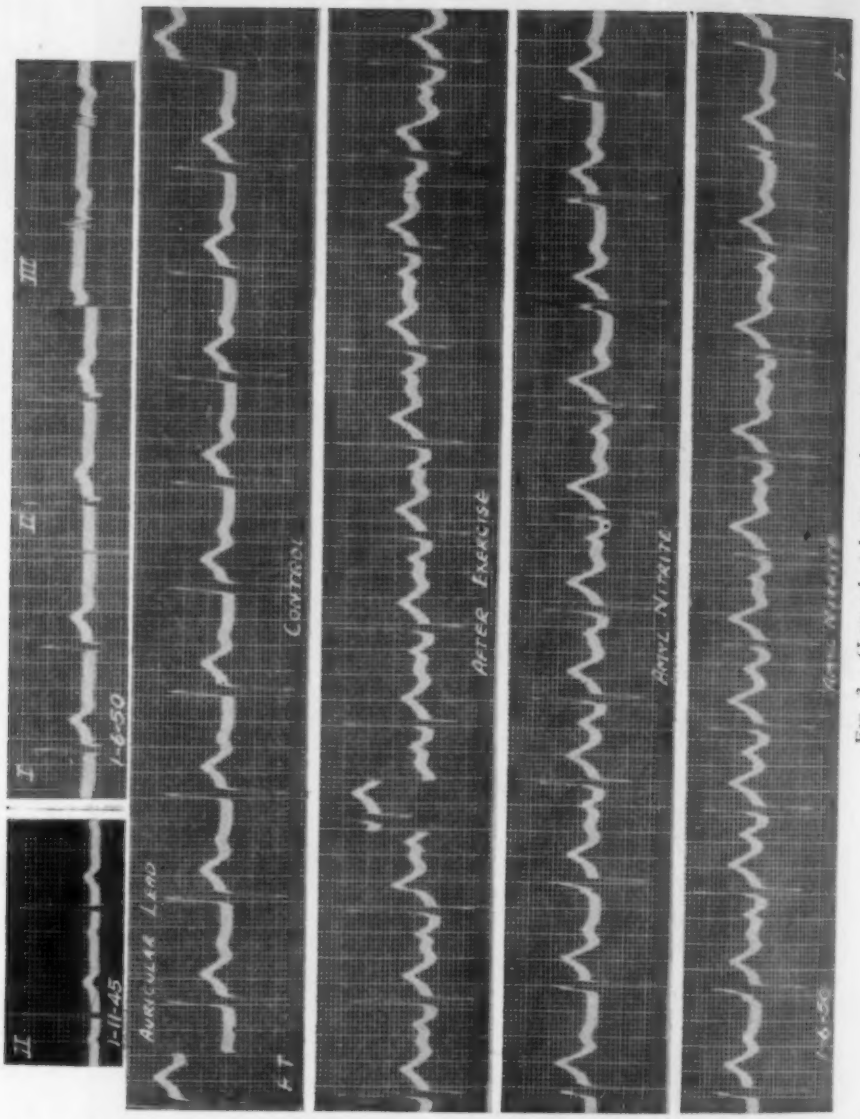

FIG. 3. (Legend at bottom of page.)

FIG. 3. Physician, aged 29 years, who had rheumatic heart disease. The standard leads taken on January 6, 1950, show no P waves. Additional auricular leads made with one electrode high along the right sternal margin and the other along the lower left sternal margin show deflections at the end of the T waves which at first were considered auricular deflections. Close inspection of Lead II shows small negative deflections not present in the records taken five years earlier. These proved to be the result of retrograde activation of the auricles and indicate atrioventricular nodal rhythm. Records taken after exercise show normal sinus rhythm with a P–R interval of 0.20 sec. Tracings taken after administration of amyl nitrite show numerous transitions from nodal to sinus rhythm, during some of which the auricle is responding in part to the sinus node and in part to the atrioventricular node.

quinidine intoxication. Quinidine therapy was discontinued. An electrocardiogram 12 hours later resembled the initial tracing. The patient was then digitalized rapidly, and conversion to normal rhythm resulted. Additional studies at that time showed that the patient had permanent right bundle branch block which, it was learned later, had been present for 13 years. This experience emphasizes again that when paroxysmal rapid heart action occurs, bizarre QRS complexes do not by themselves permit a diagnosis of paroxysmal ventricular tachycardia. The value of electrocardiographic control of the medical management of such cases is also illustrated by this patient.

The records shown in figure 3 were made on a 29 year old man who had rheumatic heart disease. The routine tracings made on January 6, 1950, showed no definite P waves. There were small, smooth deflections at the end of the T waves, especially in records over the right precordium, which were considered at first to be P waves, although they were later shown to be U waves. If they were P waves, it meant that the PR interval was longer than it had been five years earlier, and that active rheumatic carditis would have to be considered. Close inspection of the records disclosed small S waves in Lead II which were not present previously, and suggested atrioventricular nodal rhythm with retrograde activation of the auricles. The simple procedures of exercise and administration of amyl nitrite produced numerous transitions to normal sinus rhythm, during which the PR interval was of normal length. These simple maneuvers helped to confirm the diagnosis of nodal rhythm and excluded the initial considerations of active rheumatic carditis.

The Evaluation of Minor Deviations in the Form of the Electrocardiogram

Any consideration of the form of the electrocardiogram immediately raises the question of what is the normal range. Changes of minor degree which are deviations from the mean are encountered in many electrocardiograms, but their significance is still in question. It seems to me wiser and more honestly courageous to evaluate such deviations by a careful correlation with the entire clinical picture, and to advise the patient to disregard them if there are no other signs of cardiac disease, than to fall into the falsely secure practice of advising such a patient that he has coronary sclerosis or myocardial strain. It is true that this latter course will avoid the occasional errors of omission which are damaging to the physician's reputation, but many normal individuals may be done a grave wrong.

The electrocardiograms illustrated in figure 4 were taken on a 40 year old man who had had slight dyspnea on climbing stairs five years before. An electrocardiogram taken at that time was reported to indicate coronary artery disease, although there were no other symptoms. He was rejected from military service one year later, after his electrocardiograms were re-

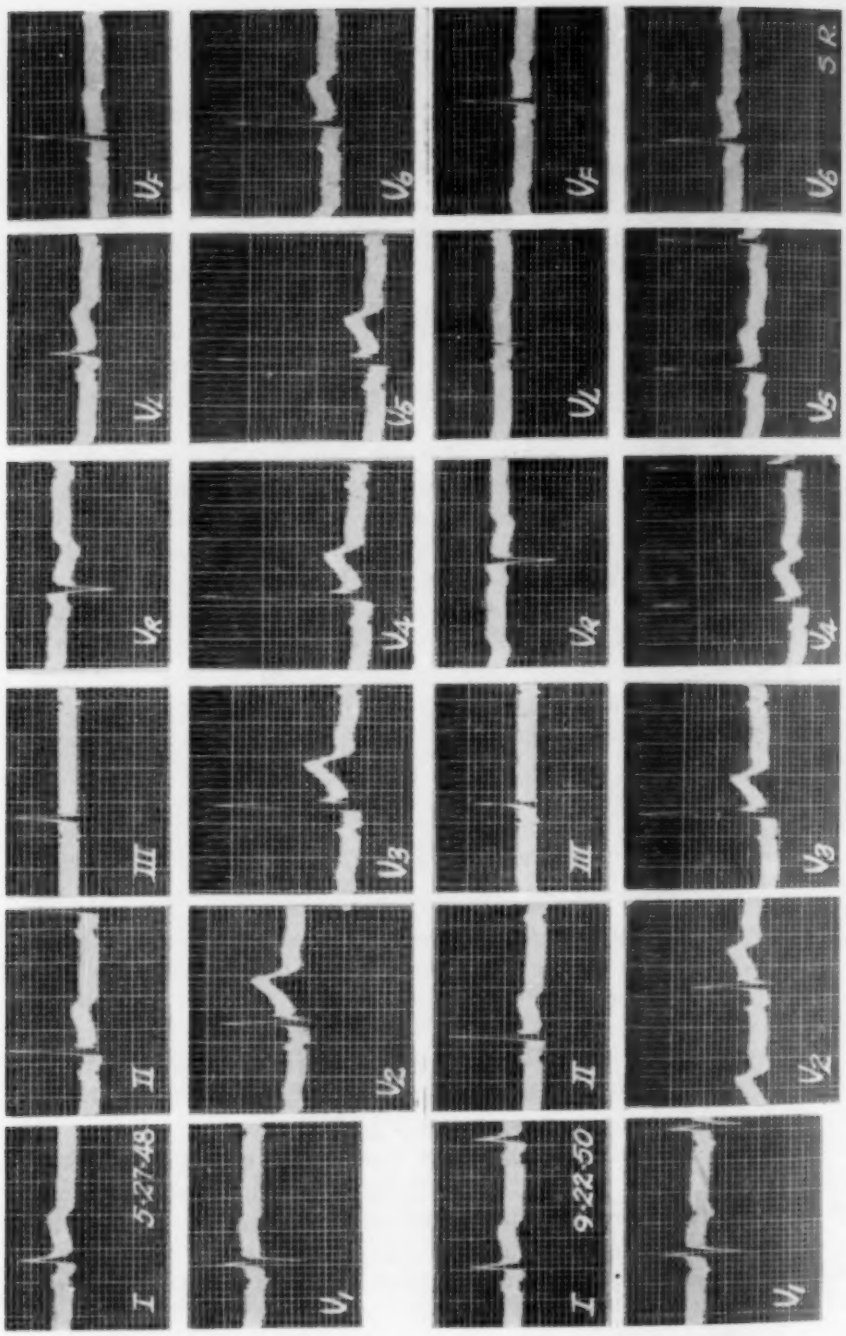

FIG. 4. Merchant, aged 40 years, who had no evidence of heart disease. May 27, 1948: There is unusual elevation of the RS–T segments in Leads I, II, V_F, V_R, V_L, V_1, V_2 and V_6. September 22, 1950: The records are very similar to those taken more than two years earlier. Numerous records taken between those shown were similar in all respects.

viewed. The initial observations in May, 1948, and the final records in September, 1950, both show a peculiar elevation of the RS–T segments in many of the derivations but especially in the precordial leads. Twelve electrocardiograms recorded between those two tracings, most of them taken at the patient's insistence, were all identical with those illustrated. All other clinical and laboratory studies have been normal and there have been no symptoms referable to the heart. It seems highly unlikely that this abnormality is evidence of any serious underlying disease.

Persistent elevation of the RS–T segments of this type occurs rather often in normal persons. It must be differentiated from the elevation of the RS–T segment which occurs in acute pericarditis, ventricular aneurysms and acute myocardial infarction. Like all deviations from the normal, such as prominent Q waves in Lead III, inversion of the T waves in Leads V_1, V_2 or even V_3, and tiny, late R′ deflections in Leads V_1 and V_2, it must be carefully evaluated and, at times, followed by means of serial observations before too much significance is attributed to it. Finally, if all other cardiac studies are normal, it should be disregarded.

The Electrocardiogram May Fail to Indicate Impending Cardiac Disaster

The place of the electrocardiogram in the diagnosis of myocardial infarction is well known to all clinicians. The electrocardiogram is the most important diagnostic laboratory aid available in problems of this category. Nonetheless, it must be remembered that serious heart disease may be present and, in fact, grave calamity may be impending, and yet the electrocardiogram will fail to indicate it. Laymen and physicians are too often falsely reassured by a normal electrocardiogram or one which shows no changes from earlier tracings.

The records shown in figure 5 are from a 48 year old man who had had an anterior myocardial infarction in 1945. All electrocardiographic signs of this lesion cleared, and the tracings recorded on October 5, 1950 are well within normal limits. Although the patient was experiencing angina pectoris of increasing severity at this time, a second electrocardiogram, taken on October 13, 1950, was identical with the first record. Four hours after the second record was taken he developed terrific precordial pain, collapsed and nearly died. Additional records on the following morning showed changes typical of a fresh posterior infarct. The electrocardiograms failed to indicate the impending disaster in this instance, although the clinical picture indicated that the patient was in serious difficulty.

Special Features of the Electrocardiogram in Myocardial Infarction

The elecrocardiographic changes resulting from some myocardial infarcts are long delayed in their appearance. Abnormalities of significance almost always do occur, but a period of two or three weeks and multiple serial ob-

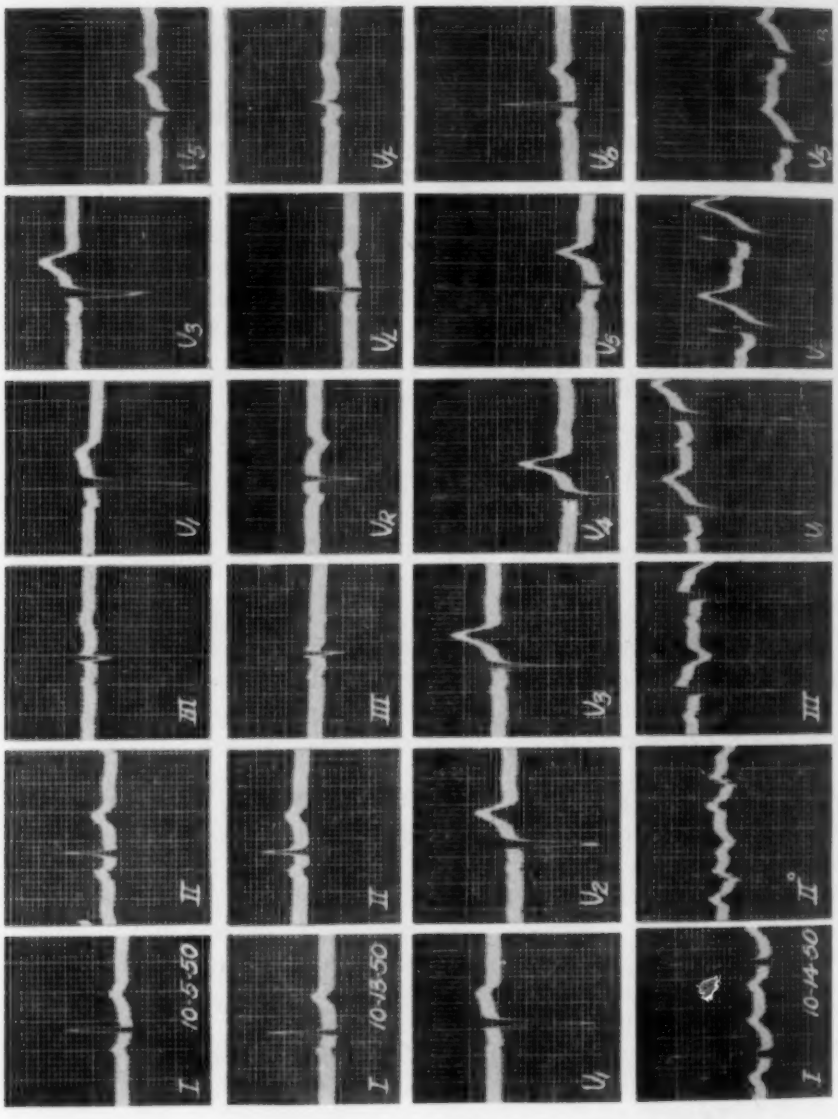

FIG. 5. Photographer, aged 48 years, who had had an anterior myocardial infarction in July, 1945. October 5, 1950: The standard and multiple precordial leads are within normal limits and show no evidence of the earlier infarct. October 13, 1950: The standard and multiple precordial leads resemble those taken eight days before. The patient was having severe angina pectoris. Four hours after this record was made he had another myocardial infarction. October 14, 1950: Tracings made 10 hours after onset of pain show signs of a fresh posterior infarct.

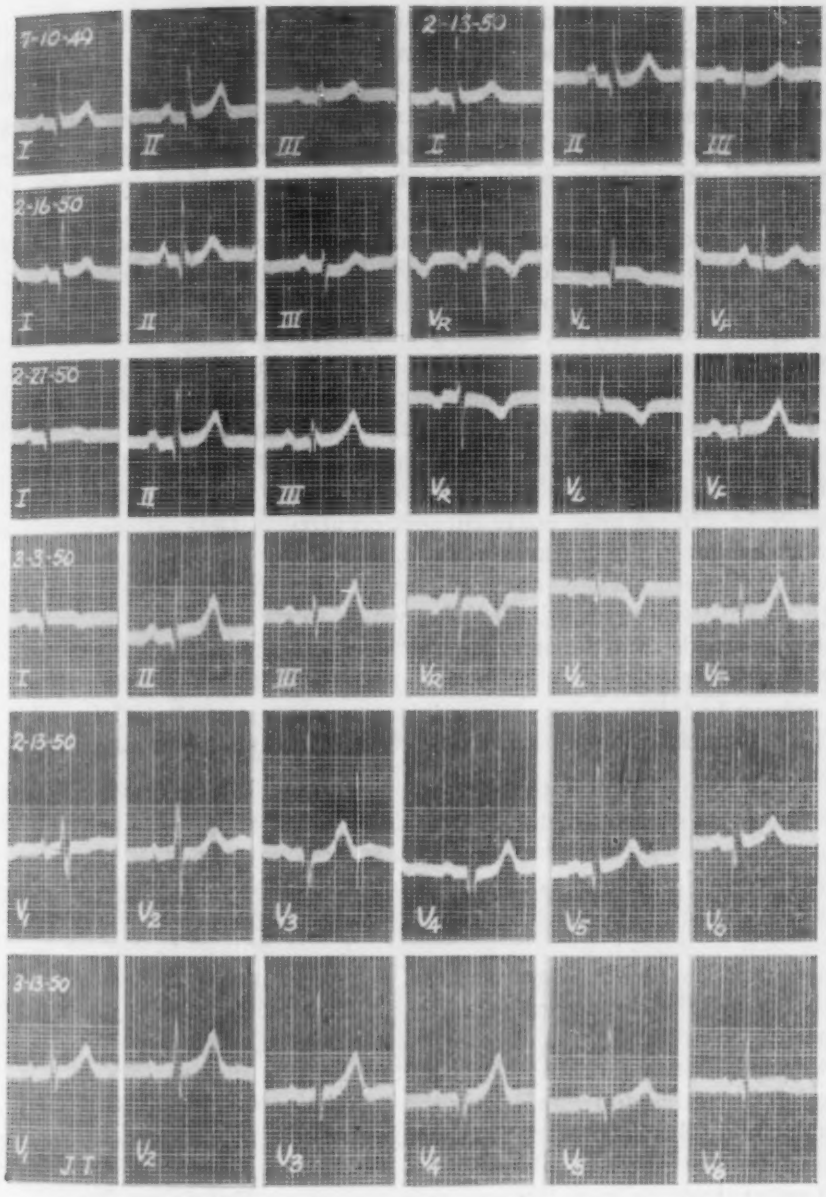

FIG. 6. Handwriting expert, aged 88 years, who had had angina pectoris for many years. A typical myocardial infarction occurred on February 12, 1950. Electrocardiograms taken the next day show no significant differences from tracings made seven months earlier. The limb leads on February 16, February 27 and March 3 show striking progressive changes in Lead V_L. The other records show only minor changes in the T waves in Leads I, III and V_6. The infarction was probably high and anterolateral in its location. (Case presented with permission of Dr. D. M. Willson.)

servations may be required. Such patients must be treated on the basis of clinical evidence, and the seeming normality of the electrocardiogram should be ignored. In addition, the alterations produced by an infarct may clear rapidly, in some patients within five to seven weeks. Consequently the diagnosis of an earlier myocardial infarction cannot always be excluded, because electrocardiograms taken relatively soon after an episode of severe pain are normal.

Some myocardial infarcts are associated with electrocardiographic changes which are confined to one or two precordial leads, to the unipolar limb leads, or to special thoracic or esophageal leads. The diagnosis in these cases is often troublesome, especially since our experience with some of the special derivations is limited. The tracings shown in figure 6 are from an 88 year old man who had had angina pectoris for many years and an acute myocardial infarction on February 12, 1950. The standard and multiple precordial leads recorded on the day after the onset were not significantly different from those taken seven months earlier. However, over the next four weeks striking progressive changes occurred in Lead V_L, together with minor changes in the T waves in Leads I and V_6. In all the tracings only Lead V_L showed changes of diagnostic significance. This was probably a high anterolateral myocardial infarct, which would have been demonstrable in records made over the anterolateral aspects of the left hemithorax two or three intercostal spaces higher than the points routinely explored.

The Electrocardiogram Does Not Measure Cardiac Reserve

There is no element in the electrocardiogram which is a direct measure of the functional capacity of the heart. The cardiac function may be entirely normal even though the form of the tracing is grossly abnormal. This is well illustrated in the instances of complete bundle branch block which apparently represent some minor congenital anomaly in the specialized conduction tissues. On the other hand, the electrocardiogram may be within the normal range in patients with congestive heart failure or incapacitating angina pectoris. Since the electrocardiogram is an inadequate measure of functional capacity, electrocardiographic interpretations in which the phrases *insufficiency* and *strain* figure may be misleading because such phrases imply a reduction in cardiac function. It is the correlation of clinical, electrocardiographic and other laboratory data which gives the true picture.

Limitations of the Electrocardiogram in Etiologic Diagnosis

The electrocardiogram permits etiologic diagnoses only under special circumstances and then only by inference based upon clinical experience. It is upon such inferences that the anoxia and exercise tests for coronary artery disease are based. Similar observations have made possible the detection of chemical derangements such as hypopotassemia, hypocalcemia and hyper-

potassemia. It is my belief that most observers who have a broad contact with the general level of electrocardiographic interpretation now current will agree that such terms as coronary sclerosis, coronary disease, and myocardial strain are much abused. Electrocardiographic changes generally attributed to coronary artery disease may be simulated by many other disorders.

The electrocardiograms illustrated in figure 7 show changes in the QRS complexes of Leads II, III, V_F and V_6 which are quite strongly suggestive

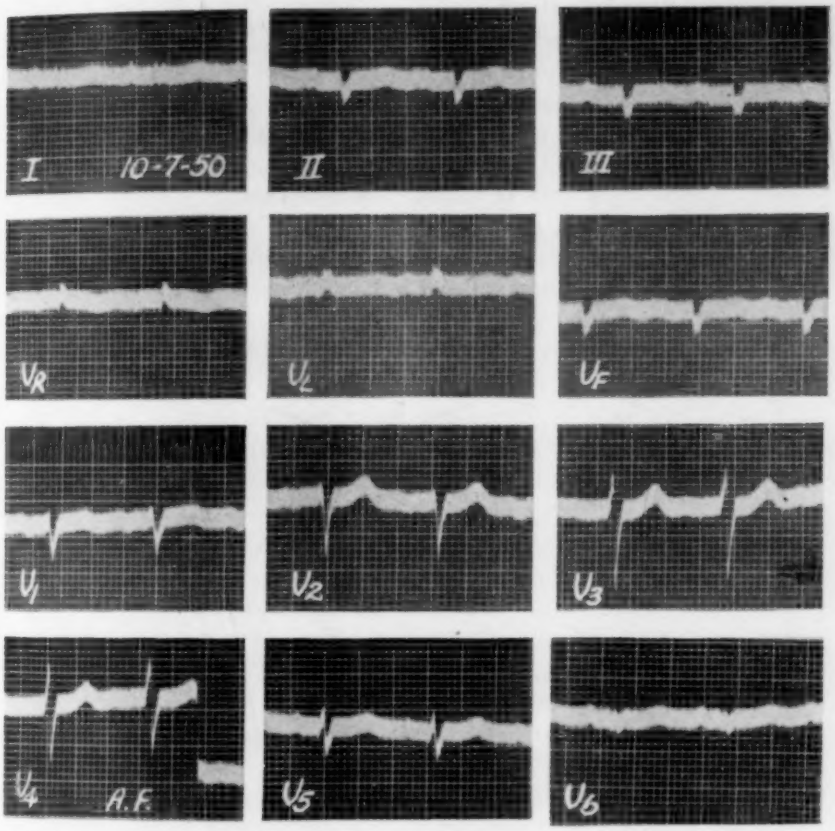

FIG. 7. Industrialist, aged 54 years, who had primary systemic amyloidosis. The prominent QS deflections in Leads II, III and V_F and the small bizarre QRS complexes in Lead V_6 resemble the abnormalities seen in some old posterolateral myocardial infarcts. Patient died seven years after first appearance of symptoms. Final course was unaffected by large doses of cortisone.

of an old posterolateral myocardial infarction. These records were taken from a 54 year old man who had primary systemic amyloidosis, undoubtedly with myocardial involvement. The diagnosis was confirmed by multiple biopsies. The patient died seven years after the onset of the disease. His terminal course was unaffected by cortisone administered in large doses over a period of three months.

Conclusion

This presentation is intended as a plea for sanity in electrocardiographic interpretation. It should not be considered a recommendation for a reactionary or overly conservative policy toward the application of new electrocardiographic information or technics to our clinical problems. The electrocardiogram is in its proper place in cardiac diagnosis when it is correlated with all of the other clinical and laboratory information which can be obtained in that particular patient.

MEDIASTINAL EMPHYSEMA OCCURRING WITH THERAPEUTIC PNEUMOPERITONEUM: REPORT OF TEN CASES *

By MILTON N. TOWBIN, M.D.,† *Denver, Colorado*

I. REVIEW OF THE LITERATURE

FOR over a hundred years physicians have recognized that mediastinal emphysema may occur following severe straining, pulmonary disease or trauma of the chest. Laennec [1] in 1819 briefly referred to this complication in his first treatise on diseases of the chest, and in 1826 accurately described it under the heading "Emphysème Interlobulaire du Poumon." [2] These observations were later confirmed by Skoda,[3] and in 1856 Rokitansky [4] explained the pathologic anatomy of this condition resulting from ulceration of the trachea or pulmonary trauma. Müller [5] in 1888 discussed its diagnostic features and also postulated a mechanism of production similar to present concepts.

Mediastinal emphysema may be found as a complication in a great variety of conditions. Laennec [2] noted that an important predisposing factor in its formation was "sustained holding of the breath during forceful and prolonged exertion." It may develop with the intense expiratory effort of severe coughing, parturition, violent exercise or blowing against an obstruction.[5 to 17] Atelectasis induced by an obstructive growth in the lumen of a bronchus, aspiration of a foreign body, or inspissated secretions which cannot be expelled from an airway often produces this syndrome.[18 to 23] It has been described in association with diseases of the respiratory tract such as influenza, pneumonia, bronchial asthma, silicosis, tuberculosis, diphtheria, measles and small-pox.[24 to 42] Exposure to pulmonary irritants, wounds of the face and neck, injury to the upper air passages or esophagus, and penetrating or nonpenetrating injury of the chest may cause it.[38, 43 to 50] Surgical procedures involving the neck and thorax, positive pressure during resuscitative or anesthetic measures, and therapeutic pneumothorax are additional etiologic factors.[38, 51 to 65]

Recently Hamman [66 to 69] called attention to the occurrence of spontaneous mediastinal emphysema, and since his classic description of its clinical features numerous case reports have been published.[70 to 93]

However, medical literature infrequently records mediastinal emphysema produced by atopic air from below the diaphragm. Demarquay [95] was the first to describe cutaneous emphysema occurring after solution of continuity

* Received for publication July 10, 1950.

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in the stomach or the intestinal canal. He believed that perforating or nonperforating traumata of the abdominal wall or the intestinal canal, accompanied by injury to the parietal peritoneum, allowed free air to enter the abdominal cavity. Roger [96] discussed the case of a tuberculous perforating ulcer of the intestine associated with subcutaneous emphysema. He concluded that this type of emphysema developed only if the lesion was located in a portion of the intestinal tract which either was not covered by peritoneum or had become adherent to the parietal portion. Erichsen [97] in 1860 observed a patient with a puncture of the bladder through the rectum who developed perineal emphysema which spread to the entire upper part of the body, while Newman [98] in 1868 recorded an instance of generalized subcutaneous emphysema occurring in a patient who died a few hours later from a ruptured viscus. Poensgen [99] studied a case with the internist Kussmaul and the pathologist Von Recklinghausen. In this patient a gastric perforation occurred near the cardia with an extension through the muscular fibers of the esophagus. Kussmaul postulated that the gas reached the mediastinum through the split fibers of the esophagus, whereas Von Recklinghausen maintained that the gas traveled subperitoneally from the ulcer to the diaphragm, migrated to either the anterior mediastinum or the retroperitoneal space and then extended into the subcutaneous tissues. In Faber's [104] patient, an ulcer on the lesser curvature of the stomach penetrated into the mediastinum through the posterior part of the diaphragm, with consequent mediastinal and subcutaneous emphysema, while Ewald [105] mentioned emphysema occurring similarly in a patient in whom a subphrenic abscess had ruptured through the diaphragm. Nelson [100] performed a laparotomy on a patient with intestinal obstruction. "As soon as the peritoneum was opened odorless gas immediately rushed forth and the abdomen became flat. No ulcer was found, but 12 hours after closing the abdominal wall generalized subcutaneous emphysema developed as a result of incising the peritoneum." Andrews, Hailes, Hayes and others [106 to 111] have described generalized emphysema appearing after rupture of the intestine due to insufflation of the rectum by compressed air. These accidents usually occurred by way of "practical jokes" when fellow workers placed the end of a pipe carrying compressed air close to the buttocks and released the valve. The funnel action of the perineal region conducted the air through the anal sphincter, with resultant laceration of the rectosigmoid junction or the sigmoid colon. Speed [112] reported an instance of a patient in whom injuries incurred in a car accident were accompanied by an extraperitoneal rupture of the rectum. Generalized emphysema appeared, spreading from the clavicle to the toes and infiltrating especially the loose areolar tissue beneath the dartos tunic of the scrotum. Vigyázó [113] attended a tabetic patient in whom it was difficult to differentiate between peritonitis and a tabetic crisis. One-half hour prior to laparotomy, umbilical subcutaneous emphysema was noted, and after surgical exploration a pin head, perforating, calloused ulcer was found on the anterior wall of the duodenum. Podlaha [114] described a patient with sub-

cutaneous emphysema in the left supraclavicular fossa, the jugular notch and the anterior thoracic wall, in whom a perforated ulcer was discovered high on the lesser curvature of the stomach. In McCorkle and Stevenson's [101] patient, a penetrating duodenal ulcer produced pneumoperitoneum and emphysema of the mediastinum, neck, chest walls, axillae and upper extremities. Jessup's [38] patient sustained an accidental rent in the diaphragm during abdominal surgery, with consequent sucking of air into the posterior mediastinum. Brown and Fine [115] record the case of a patient who was given a double contrast enema and then developed extensive subcutaneous emphysema extending from the rectum to the base of the skull and infiltrating the retroperitoneal space, the anterior mediastinum and the paravertebral spaces of the neck.

Artificial introduction of gas into the abdominal cavity by means of a needle puncture is an old procedure, for the intraperitoneal injection of oxygen was recommended in the treatment of tuberculous peritonitis by Von Mosetig-Moorhof [116] as early as 1893. Smith [117] reported "witnessing, in 1924 or 1925, a pneumoperitoneum induced for radiographic studies of tuberculous mesenteric glands in a young woman. As soon as induction began she became dyspneic and complained of chest pain. She then collapsed and died soon thereafter. Postmortem examination revealed bilateral pneumothorax with collapse of both lungs. A number of small holes were discovered in the diaphragm connecting the peritoneal and both pleural cavities."

It was not until 1931 that the possibility of using pneumoperitoneum for the treatment of pulmonary tuberculosis was first realized, when Banyai [118, 119] accidentally injected air into the abdominal cavity of one of his patients while attempting to give artificial pneumothorax. Since then artificial pneumoperitoneum has become a common collapse measure employed in the treatment of pulmonary tuberculosis.[120 to 156] The complications usually encountered with this procedure are nausea, vomiting, generalized abdominal pain, obliterative peritonitis, serofibrinous peritonitis, ascites, air embolism, peritoneal shock, perforation of a viscus, incarcerated femoral hernia, aggravation of an inguinal, umbilical or postoperative hernia, and acute appendicitis. In addition, rupture or atrophy of the diaphragm,[123, 125, 144] aggravation of preëxisting heart disease,[134] dysmenorrhea,[147] hemorrhage from the rectum,[147] scrotal pneumocele [123, 141] and massive atelectasis [125, 126] have been reported.

Mediastinal emphysema accompanying induced pneumoperitoneum is a rare development. Although often mentioned as a possible complication, it has been clearly recorded in only 15 instances, as follows: One case by Clifford-Jones and MacDonald [137]; one case by Anderson and Winn [144]; seven cases by Banyai and Jurgens [149, 150]; four cases by F. A. H. Simmonds [151]; one case by Moyer,[155] and a case briefly mentioned by Jehn and Nissen.[157] Therefore, mediastinal emphysema occurring with therapeutic pneumoperi-

toneum in 10 patients at this hospital during the past 14 months seems worth reporting.

II. Case Reports

Case 1. An 18 year old white man; moderately advanced pulmonary tuberculosis; received streptomycin; pneumoperitoneum; routine refill; one hour later cervical and scrotal emphysema; dysphagia; dysarthria; auscultatory and roentgenographic signs of mediastinal emphysema.

This man was admitted to the hospital October 9, 1948, with moderately advanced pulmonary tuberculosis. After he had been given streptomycin a right pneumothorax was induced, but it was abandoned because of an apical pleural symphysis. On January 24, 1949, an artificial pneumoperitoneum was induced uneventfully. Routine refills of 750 c.c. of air were given on January 26 and January 27, 1949, respectively. On February 1 a routine fluoroscopic examination showed that the air in the peritoneal space had elevated the diaphragms to the level of the ninth posterior rib bilaterally. He received 1,000 c.c. of air, and the final pressure reading ranged from 10 to 14 cm. of water. One-half hour later he complained of mild diffuse abdominal discomfort, accompanied by stiffness and pain at the angle of the jaw on opening his mouth. Within one hour he noticed hoarseness, dysphagia and scrotal swelling. Physical examination disclosed crepitation in the neck and scrotal tissues, with swelling of the scrotum. There was no subcutaneous emphysema along the lateral chest wall or adjacent to site of insertion of the needle in the abdominal wall. Examination of the heart revealed that the point of maximal impulse was not visible and precordial dullness was diminished. On auscultation one heard indistinct heart tones associated with a peculiar crunching, crackling noise synchronous with systole. This bizarre sound could be heard over the entire precordium and was unrelated to the patient's position or the phase of respiration. Temperature, pulse, respiration and blood pressure readings were not significantly altered. He was unaware of this precordial crunching, nor could it be heard at the bedside without a stethoscope. Fluoroscopic examination showed an area of increased lucency sharply defined by a white line parallel to the left cardiac border. A similar shadow was noted extending into the superior mediastinum and periaortic region. Cardiac pulsations were normal and roentgenograms of the chest confirmed the fluoroscopic findings. These studies were compatible with the diagnosis of mediastinal emphysema occurring with a pneumoperitoneal refill. Electrocardiograms, phonocardiograms, blood counts and sedimentation rates were performed but were not remarkable. During the next 48 hours his subjective symptoms disappeared and the crepitation in the neck and the scrotum diminished. The mediastinal crunch persisted for several days, becoming less audible after the third day. Pneumoperitoneum was again induced and has been maintained without difficulty.

Case 2. A 30 year old white man; moderately advanced pulmonary tuberculosis; streptomycin therapy; pneumoperitoneum; severe coughing episode; pain on turning head; sudden hoarseness; muffled voice; dysphagia; cervical emphysema; auscultatory signs of mediastinal emphysema; roentgenographic evidence only of subcutaneous emphysema in neck.

This soldier entered the hospital because he had moderately advanced pulmonary tuberculosis with cavitation in the left lower lobe. Following streptomycin therapy, a pneumoperitoneum was uneventfully induced. During the next month he received weekly refills of air with no difficulty. Forty-eight hours after the administration of 900 c.c. of air he complained of "pain and tightness about my neck on turning my head from side to side" and of "hoarseness with difficulty in swallowing." We noted that the tone of his voice had changed from a distinct nasal twang to one that was indis-

tinct and muffled. These symptoms had suddenly appeared that morning following a severe bout of coughing. Physical findings disclosed crepitation in the tissues of the neck, with no subcutaneous emphysema present either along the lateral chest wall or in the scrotum. Examination of the heart revealed a diffuse point of maximal impulse and resonance to percussion of the precordial area. On listening to the heart with the patient supine, mediastinal crepitation synchronous with systole was audible along the left sternal border. With the patient in the erect position, however, these adventitious sounds disappeared. They could not be heard with the unaided ear, and the patient was not aware of this unusual crackling. Temperature, pulse rate, respiration, blood pressure, electrocardiograms, blood counts and sedimentation rates were not remarkable. Fluoroscopic examination of the heart and lungs showed nothing significant; however, roentgenograms of the neck and chest revealed "air streaks" of subcutaneous emphysema in the cervical tissues. His subjective symptoms rapidly subsided and collapse was continued.

Case 3. A 19 year old white man; bilateral pulmonary tuberculosis with cavitation; received streptomycin; initial pneumoperitoneum; three hours later emphysema in scrotum and along chest wall; no cervical crepitation; auscultatory and roentgenographic evidence of mediastinal air.

This patient entered the hospital with the diagnosis of moderately advanced pulmonary tuberculosis. When streptomycin therapy was completed, pneumoperitoneum was recommended. Three hours after establishing this collapse measure the patient noted palpable emphysema along the left lateral chest wall. Scant attention was paid to this finding, for it was believed that air was seeping through the needle tract in the abdominal wall. Shortly thereafter he complained of difficulty in talking and swallowing. Physical examination failed to reveal any emphysema in the cervical tissues; however, crepitation was present in the tissues of the left lateral and anterior chest walls and in the scrotum. Cardiac examination disclosed a diffuse point of maximal impulse, absence of precordial dullness to percussion, distant heart tones and a distinct mediastinal crunch. The patient was quite apprehensive but was unaware of any unusual heart sounds, nor could the crackling be heard with the unaided ear. Fluoroscopic and roentgenographic studies confirmed the presence of mediastinal air. These signs and symptoms rapidly subsided during the next few days. The pneumoperitoneum was again induced a week later and has been maintained with no repetition of pneumomediastinum.

Case 4. A 19 year old white man; far advanced pulmonary tuberculosis; streptomycin therapy; pneumoperitoneum; routine air instillation; 24 hours later, hoarseness and dysphagia; cervical and scrotal emphysema; auscultatory and roentgenographic evidence of mediastinal air.

This 19 year old corporal was admitted to the hospital because he had far advanced pulmonary tuberculosis. After four months of streptomycin therapy he showed marked improvement and pneumoperitoneum was uneventfully induced on May 2, 1949. Routine air injections, consisting of 750 c.c. of air, were given intraperitoneally on May 3 and 4. Twenty-four hours later the patient had difficulty in talking and in swallowing his food. Physical findings disclosed crepitation in the tissues of the neck and scrotum, but no emphysema was felt along the lateral chest wall. Mediastinal crepitation was distinctly heard on cardiac auscultation only in the erect position. He was not uncomfortable and felt nothing unusual relative to his heart. The mediastinal crackles were not loud enough to be audible at the bedside without a stethoscope. Fluoroscopic and roentgenographic studies confirmed the diagnosis of pneumomediastinum. Dysphagia and subcutaneous and scrotal emphysema disappeared rapidly, but the precordial crunch persisted for several days. Pneumoperitoneum was again induced and has been maintained.

Case 5. A 20 year old white man; moderately advanced pulmonary tuberculosis; streptomycin therapy; pneumoperitoneum induction difficult; several different sites attempted; one hour later, cervical and scrotal emphysema; dysphagia; hoarseness; auscultatory and roentgenographic signs of mediastinal air.

This man entered this hospital with moderately advanced pulmonary tuberculosis. After he had been given streptomycin therapy, pneumoperitoneum was induced. During the procedure it was noted that elevated pressure readings persisted even though the oscillations of the pressure gauge needle indicated proper insertion of the needle. Several points of entry were attempted, with similar results. Because of these increased pressure readings, only 600 c.c. of air were instilled, and a final pressure reading of 18 cm. of water was obtained. Within an hour the patient became apprehensive and complained of dysphagia and dysarthria. Physical examination revealed scrotal emphysema and crepitation in the cervical and gluteal tissues. On listening to the heart, one heard sounds compatible with mediastinal emphysema. The mediastinal crepitation was heard with the patient in all positions, and he was aware of a "grinding noise around my heart, especially when I sit up." He did not "feel" the sound when lying down, nor was it audible with the unaided ear. Fluoroscopic and roentgenographic studies confirmed the diagnosis of mediastinal air. The emphysema subsided rapidly and the peculiar crunching disappeared after 48 hours. Pneumoperitoneum was again induced with no difficulty.

Case 6. A 24 year old white man; bilateral pulmonary tuberculosis; streptomycin therapy; left pneumothorax unsuccessful; pneumoperitoneum; routine refill; 60 hours later, peculiar sore throat; straining at stool; peripherovascular shock; subcutaneous emphysema in cervical tissues; auscultatory and roentgenographic evidence of mediastinal emphysema.

This sergeant entered the hospital because of bilateral pulmonary tuberculosis. After he had been given streptomycin therapy a left pneumothorax was attempted, but it was abandoned because an adhesion in the left apex was inoperable. On July 11, 1949, a pneumoperitoneum was successfully induced. Forty-eight hours later he was given his first peritoneal refill, consisting of 900 c.c. of air, and he received a similar amount of air the following day. Approximately 60 hours later he told the night charge nurse, "I have a peculiar soreness way down inside my throat and I can't seem to swallow comfortably. This does not feel like a real sore throat, but seems to go farther down. In addition, I can't feel the air in my stomach as much as I could previously." He spent a comfortable night, but on arising the next morning he still felt "this unusual sore throat." While straining at stool that morning he suddenly complained of marked vertigo and began to perspire freely. He rapidly turned pale; his pulse rate of 120 became irregular, his blood pressure dropped to 85 mm. Hg systolic and 60 mm. diastolic, and he appeared to be in mild peripherovascular shock. There was no evidence of mediastinal emphysema. After receiving supportive measures he felt comfortable, stating, "the soreness in my throat has suddenly disappeared." His pulse was again regular and the blood pressure readings returned to normal. On reexamination, subcutaneous emphysema was present in the cervical tissues, but no crepitation was present along the lateral chest wall or in the scrotum. On listening to the heart (with the patient in all positions), mediastinal crepitation was easily heard. He was unaware of this adventitious sound, nor could one hear it without a stethoscope. Fluoroscopic and roentgenographic studies revealed a radiolucent area parallel to the left border of the heart, and these findings confirmed the impression of mediastinal emphysema. The symptoms subsided rapidly and pneumoperitoneum has been maintained.

Case 7. A 23 year old colored man; bilateral tuberculous infiltrations; received streptomycin; right pneumothorax unsuccessful; right phrenemphraxis with pneumo-

peritoneum; routine refill; eight hours later difficulty in opening mouth, talking, and swallowing; subcutaneous emphysema in cervical tissues; auscultatory and roentgenographic evidence of mediastinal emphysema.

This man was hospitalized because a routine extension-of-service roentgenogram disclosed bilateral tuberculous infiltrations. After he had been given streptomycin therapy a right pneumothorax was induced, but it was abandoned because adhesions in the right apex were inoperable. Following a right phrenemphraxis a pneumoperitoneum was uneventfully induced. The next day he received a refill of 900 c.c. of air and approximately eight hours later the patient noted "difficulty in opening and closing my mouth and some discomfort in talking and swallowing." However, he paid scant attention to these symptoms and spent a quiet night. The following morning he complained of inability to swallow and of pain along the right thigh. Physical examination revealed subcutaneous emphysema along the medial aspect of the right thigh and crepitation in the tissues of the neck. No mediastinal crunch was elicited, nor was the scrotum enlarged. Fluoroscopic examination showed nothing significant. Throughout the day the heart was examined frequently, but mediastinal crepitation was not heard. The following morning, however, on examining the heart, mediastinal crunching was audible. Fluoroscopic and roentgenographic studies at this time confirmed the presence of pneumomediastinum. The symptoms persisted for several days, and the mediastinal crunch was best elicited with the patient in the erect position. At no time was he aware of this peculiar sound, nor was it audible to others at the bedside without a stethoscope. Pneumoperitoneum treatment was resumed with no recurrence of this complication.

Case 8. A 21 year old white man; moderately advanced pulmonary tuberculosis; streptomycin therapy; pneumoperitoneum; severe coughing paroxysm; sudden muffled voice; dysarthria; dysphagia; emphysema in cervical tissues; auscultatory and roentgenographic signs of mediastinal air.

This patient was admitted to a station hospital complaining of nausea and vomiting of eight days' duration. A diagnosis of a peptic ulcer was made and medical management instituted. Despite relief from the gastric distress, anorexia and malaise persisted. Roentgenograms of the chest and sputum examinations confirmed the diagnosis of pulmonary tuberculosis. Following a course of streptomycin therapy, a pneumoperitoneum was induced and maintained without difficulty. Five months after the collapse measure had been established the patient uneventfully received the customary weekly injection of 900 c.c. of air intraperitoneally. The next morning he experienced a severe episode of "choking and coughing," and when this had subsided he noticed a "queer, choking sensation in my throat, and my voice has a nasal twang." Shortly thereafter he complained of pain about the tissues in his neck. Physical examination revealed crepitation in the tissues of the neck, with no palpable subcutaneous emphysema along the lateral chest wall, in the periumbilical area or in the scrotal tissues. On listening to the heart, mediastinal crepitation was audible but could not be heard without a stethoscope. Fluoroscopic and roentgenographic studies confirmed the diagnosis of pneumomediastinum. Within 96 hours the signs and symptoms subsided and pneumoperitoneum has been continued to the present time.

Case 9. A 26 year old white man; moderately advanced pulmonary tuberculosis; streptomycin and PAS therapy; pneumoperitoneum; routine refill; one-half hour later, weakness and profuse sweating; dysarthria; dysphagia; cervical emphysema; auscultatory and roentgenographic signs of mediastinal emphysema.

This corporal entered the hospital with a diagnosis of moderately advanced pulmonary tuberculosis. After he had received streptomycin and para-aminosalicylic acid for 120 days, there was evidence of roentgenographic and clinical improvement. On February 1, 1950, a pneumoperitoneum was induced with the injection of 900 c.c.

of air. The patient was completely comfortable throughout this procedure and the pressures were not remarkable. Seventy-two hours later a routine refill of 900 c.c. of air was given with no difficulty. On returning to bed the patient felt "very weak" and began to perspire freely. He had difficulty in talking and swallowing, and was unable to eat his noon meal because of "a peculiar soreness in my throat." Although this discomfort persisted during the entire day he did not believe it warranted the attention of his ward officer. When he was examined the following morning some of his distress had subsided, but palpable crepitation was marked in the cervical tissues. Auscultation of the heart disclosed the typical crunching noise of mediastinal emphysema. This sound could be heard best with the patient either in the left lateral recumbent position or sitting erect bending slighly forward. Fluoroscopic and roentgenographic studies confirmed the presence of mediastinal air. At no time was he aware of this peculiar mediastinal crunch, nor could one hear it at the bedside with the unaided ear. These signs persisted for approximately 96 hours, although the mediastinal crackle was not clearly audible after 24 hours. Collapse was again uneventfully induced.

Case 10. A 23 year old white man; moderately advanced pulmonary tuberculosis; combined drug treatment; refill of pneumoperitoneum; three hours later muffled voice; hoarseness; dysphagia; auscultatory and roentgenographic evidence of mediastinal air.

This corporal entered the hospital with the diagnosis of moderately advanced pulmonary tuberculosis. When combined intermittent treatment with streptomycin and para-aminosalicylic acid was completed, pneumoperitoneum was recommended. Three hours after a routine refill the patient noted that "the sides of my throat feel a little sore; my voice sounds as if it is coming through my nose, and I feel a peculiar soreness way down in my throat." The tone of his voice had become muffled. Physical examination disclosed marked crepitation in all the cervical tissues. On auscultation of the heart, typical sounds of mediastinal crunching were distinctly audible and were best heard when the patient sat erect and leaned forward. Fluoroscopic and roentgenographic studies showed distinct "air streaks" in the cervical tissues and an area of increased radiolucency adjacent to the left heart border. These signs and symptoms gradually subsided and pneumoperitoneum was continued with no further difficulty.

III. Pathogenesis

Mediastinal air may originate from sources located either above or below the diaphragm.

From above the diaphragm, air may reach the interpleural space along the fascial planes of the neck, through a perforation of the trachea, bronchus or esophagus into the mediastinum, and from the interstitial tissues of the lungs.[69]

Trauma to the face, neck, upper respiratory passages or the esophagus allows air to be blown directly into the mediastinum. The Macklins [162] stress the point, however, that "surgical" emphysema frequently appears before an operation is performed, although this procedure is often blamed for the escape of air into the tissues.

Pulmonary interstitial emphysema is produced when air is released from ruptured alveoli into the connective tissue septa of the lung. We must credit Laennec [2] for first accurately describing the pathologic anatomy of interstitial emphysema and spontaneous pneumothorax, although he did not specifically identify these conditions. In postmortem studies he found projec-

tions or bulges on the visceral pleura, and concluded that severe coughing, prolonged exertion or trauma tore distended alveoli, thus permitting air to pass through the septa to the pleura and form an emphysematous vesicle. If such a bulla ruptured, it may have caused a spontaneous pneumothorax. Müller [5] summarized the course of events as follows: "As a result of forceful coughing, disruption of alveolar walls occurs and air is forced into the pulmonary interstitial tissues. The entrapped bubbles may advance along the peribronchial and perivascular sheaths either directly toward the hilus or they may dissect beneath the pleura (elevating it in the form of a bleb) before continuing subpleurally into the hilus of the lung. The loose meshes of the mediastinum are thus infiltrated, and the pericardial sac, large vessels, trachea and esophagus become surrounded by bubbles of air which frequently spread between the costal pleura and the ribs before halting at the insertion of the diaphragm. In none of my collected cases did air travel through the diaphragm into the abdominal cavity. The escaping air dissects along the trachea and great vessels into the supraclavicular fossae and then proceeds to cover a large part of the body surface with subcutaneous emphysema."

Berkley and Coffen [24] reported finding extensive subcutaneous emphysema and spontaneous pneumothorax as a complication of influenzal pneumonia. Palpable crepitation was present over the neck, face, scalp, chest, trunk, scrotum and thighs. They proposed an intrapleural and an extrapleural route for the egress of the air. To travel along the intrapleural path, the air must pass through the layers of the pleura directly into the subcutaneous tissues without traveling down from the neck. For it to do this without producing a pneumothorax, they assumed that adhesions between the pleural membranes existed at some area and that the passage of air occurred at this point. Although they confirmed this pathway in only one of their cases, other observers [29, 38, 40] have suggested this short route as a probable means of producing subcutaneous emphysema. To explain the migration of air extrapleurally, Berkley and Coffen presumed that air-sacs at the periphery ruptured and that leading off from these torn alveoli were "air streaks" which followed the course of the great vessels. These "streaks" were easily identified on the roentgenogram. Dissection of the lung showed that the "air streaks" could be traced along vascular sheaths which acted as highways for the air into the hilus. By exposing the root of the lung extrapleurally without rupturing the bronchus, and submerging it in water, they demonstrated that gently squeezing the lung forced bubbles of air to the hilus, the air presumably originating from the pulmonary parenchyma around the vessel walls.

Kelman [26] examined at necropsy 20 patients who had died of influenza and found marked vesicular and interstitial emphysema. The interstitial emphysema invaded the anterior mediastinum and was also present in the perirenal tissues. After producing experimental emphysema by inflating the lungs of dead rabbits with a bicycle pump, she concluded that, first, vesi-

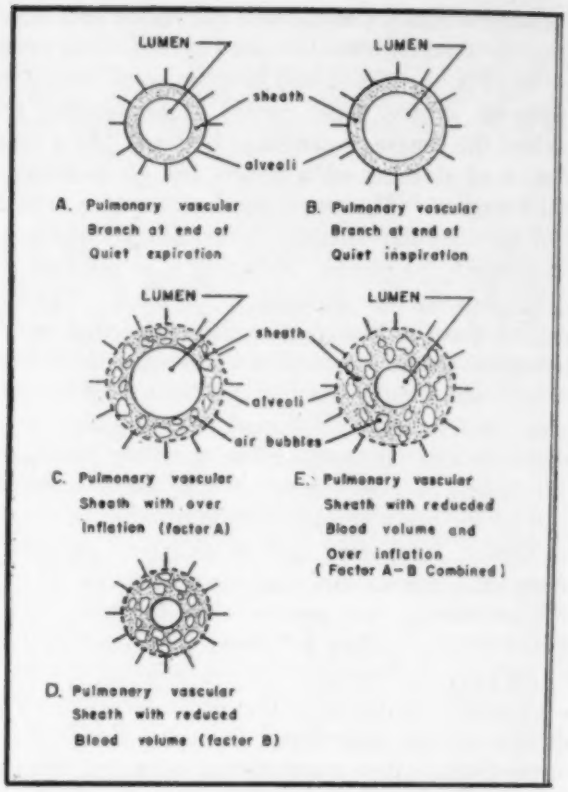

FIG. 1. In this figure the outer circle represents the bases of a ring of 12 alveoli around a blood vessel. The sides of the alveoli radiate like spokes of a wheel. The inner circle represents the endothelial wall of a blood vessel.

A. This represents the conditions at the end of quiet expiration.

B. This is the same vessel and its surrounding alveoli at the end of normal inspiration. The bases of the alveoli are stretched, the circumference of the vessel is greater as more blood flows into the lungs, but the volume of the sheath remains constant. It is a thinner rim around a wider lumen than in A.

C. This represents the conditions in overinflation. The inner circle of vessel wall is the same as in B, being dilated as in normal inspiration, but the alveoli are much distended, so that the circumference of their bases is much greater. This puts a tension on the sheath between overexpanded outer circle and normally expanded inner circle. The alveolar bases break as shown by the dotted lines, and air escapes from the alveoli into the sheath as shown by the large bubbles. This factor of overinflation we have called Factor A.

D. A strain may be put upon the sheath of the vessel creating a pressure gradient by making the inner circle smaller instead of the outer circle larger. This means a reduction in the amount of blood going through the pulmonary vessels so that the lumen is smaller. As forced expiration against obstruction is accompanied by the damming back of blood on the systemic venous side, the outer circle of alveoli is a little smaller than in normal inspiration, but not as small as in expiration where the air can escape normally from the mouth. The inner circle is much smaller than in A. Again a gradient is created, and air enters the sheath. This we have called Factor B.

E. Factors A and B may be combined; the alveoli may be over-distended, and the blood vessel caliber lessened. This heightens the gradient and induces rupture more readily.

Reproduced with permission from Macklin, M. T. and Macklin, C. C.: Malignant interstitial emphysema of the lungs and mediastinum as an important occult complication in many respiratory diseases and other conditions: An interpretation of the clinical literature in the light of laboratory experiment, Medicine 23: 281–358, 288, 1944.

cular emphysema formed, and second, when these bullae ruptured the escaped air traveled around the visceral pleura on the surface of the lung to reach the hilus.

Joannides and Tsoulos,[158] in confirming these observations, also noted that the junction of the parietal and visceral pleurae at the hilus has a loose union with the lung; when pulmonary injury was incurred, air easily escaped at this point.

Macklin and Macklin,[159 to 162] in correlating their experimental findings with clinical observations, have contributed much in extending our knowledge of the pathogenesis of mediastinal emphysema. They postulate that pulmonary alveoli are divided in two types: (a) those with their bases lying

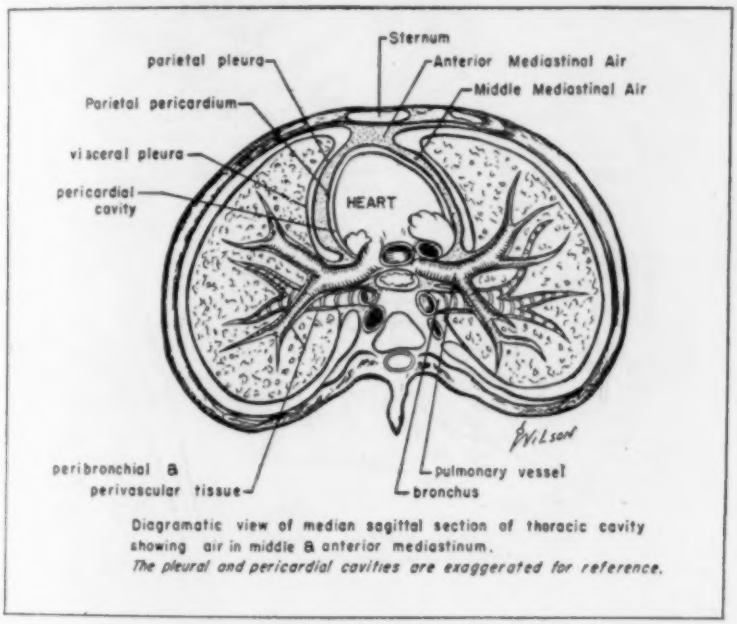

FIG. 2.

between other alveoli ("partitional" type), and (b) those whose bases rest against some structure other than the adjoining alveoli ("marginal" or "nonpartitional" type). Only the latter type, whose bases rest upon bronchi, pulmonary blood vessels, connective tissue septa or pleura, is concerned in producing pulmonary interstitial emphysema and its sequel, mediastinal emphysema. Pores which exist between the bases of "partitional" alveoli allow air to escape from one sac to another, but air released from the bases of "marginal" alveoli passes into the underlying connective tissue. The area between a "nonpartitional" alveolar base and its connective tissue sleeve is constant in volume because the space is filled with unexpansible tissue fluid.

During quiet expiration this connective tissue sheath forms the thick rim of a small circle, and in quiet inspiration it forms a thinner rim around a larger circle, but throughout the respiratory cycle the volume of this interstitial space remains constant (figure 1). The normal relationship between alveolus and tissue sheath floor can be altered by either overinflating the alveoli without corresponding expansion of the vessel lumen (Factor A),

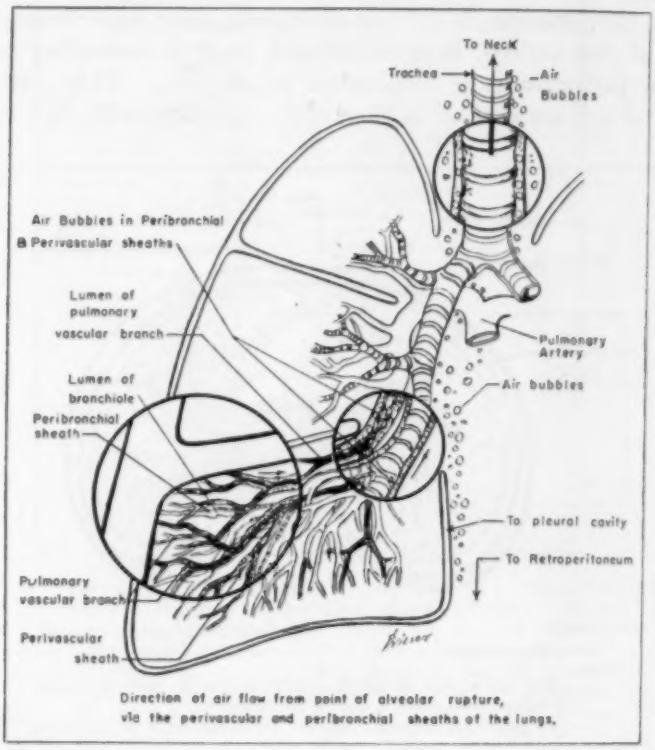

FIG. 3. A diagram to show the pathway of the air from the air spaces of the lung to the mediastinum and beyond via the perivascular and peribronchial sheaths of the lung. Bubbles of air in these sheaths and connective tissue of the mediastinum are shown as small spherules. One of the many points of invasion of the perivascular sheath is indicated by the arrows in the lung interior; and one of the sites of breaking through into the pleural cavity is also indicated by an arrow.

Modified and reproduced with permission from Macklin, C. C.: Pneumothorax with massive collapse from experimental local over-inflation of lung substance, Canad. M. A. J. 36: 414–420 (April) 1937.

or narrowing the vessel caliber without corresponding diminution in the size of the adjacent alveoli (Factor B). These factors, either alone or in combination, permit a pressure gradient to form between the alveoli and the tissue sheath. The resultant pressure gradient disrupts the alveolar bases and air escapes into the connective tissue beneath, forming pulmonary interstitial emphysema. The lengthening and shortening of the bronchi during

respiration propel the released air along the path of least resistance to the root of the lung. From the hilus the free air travels into the middle mediastinum along the pleural reflections of the pulmonary vessels to the pericardial reflections over these same structures. It dissects into the potential space between the parietal mediastinal pleura and parietal pericardium and then infiltrates the tissues of the anterior mediastinum (figure 2). The air may extend to the superior mediastinum and descend along the course of the

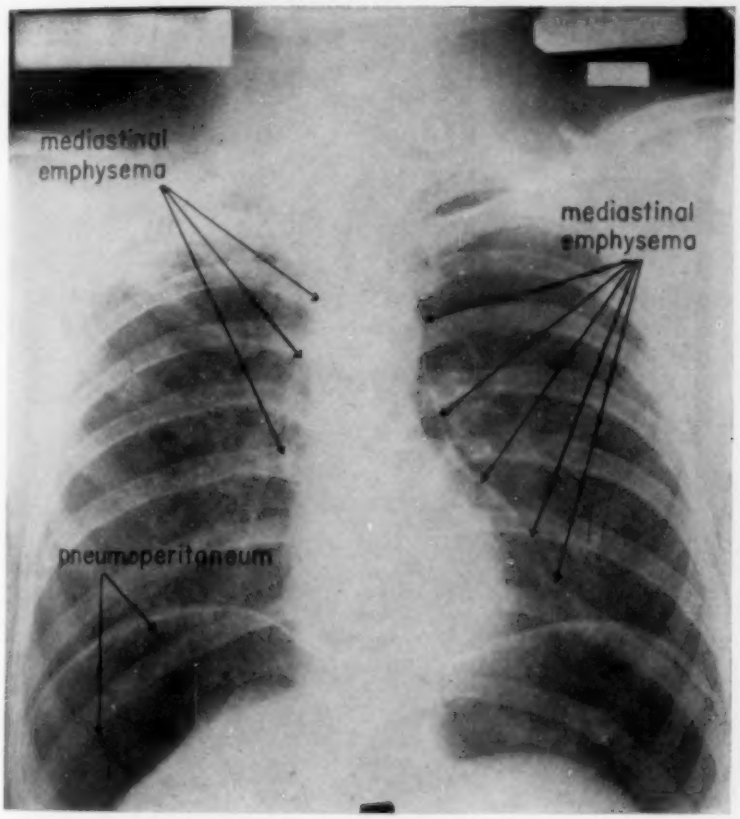

FIG. 4. Case 1.

great vessels to enter the posterior compartment. Rupture of the delicate parietal mediastinal pleura may produce a pneumothorax (figure 3). The migrating bubbles may accompany the subclavian vessels and proceed upward into the neck, face, axilla and over the chest and arms to cause generalized subcutaneous emphysema. From the posterior mediastinum the air may pass below the diaphragm along the aorta or the postesophageal areolar tissues to the mesenteries and retroperitoneal space. It may descend along the root of the mesenteries into the fascia of the iliopsoas muscle and out

through the inguinal ring, burrowing either into the tissues of the scrotum or along the superficial structures of the abdominal wall. At the region of the perirenal areolar tissues a bulla may form and rupture, allowing air to escape into the free abdominal cavity and produce pneumoperitoneum. Kelman believed the escaped air traveled from the periphery around the visceral pleura on the surface of the lung into the hilus. The Macklins, however, have shown in their ingenious experiments that disruption occurs not

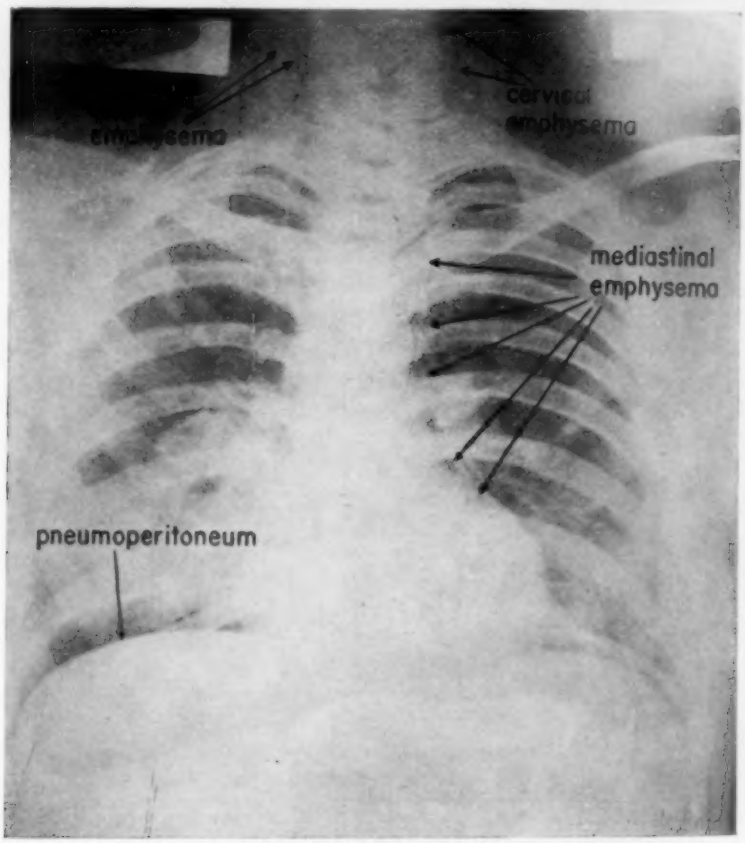

FIG. 5. Case 4.

only in the alveoli under the pleura, but also in alveoli situated throughout the lung. Not only may the air proceed medially toward the lung hilus, but it may also travel laterally into the vessel sheaths of the other lung or backward along sheaths of the same lung where there is no leakage.

Clinically Factor A, i.e., air leaking into tissue sheaths from overstretched alveoli, is produced by any atelectatic process such as bronchial obstruction, infections of the upper and lower respiratory system or pneumo-

thorax of the newborn.[162] Factor B, air leaking from hyperdistended alveoli surrounding inadequately filled blood vessels, is established clinically by (1) a lessened return of the venous blood to the right heart; (2) a failing right heart which cannot send out the normal amount of blood to the lungs; (3) stenosis or insufficiency of the pulmonary artery or valve, and (4) an obstruction of the pulmonary artery, as in pulmonary embolism. In many instances, lessened return to the right heart is associated with in-

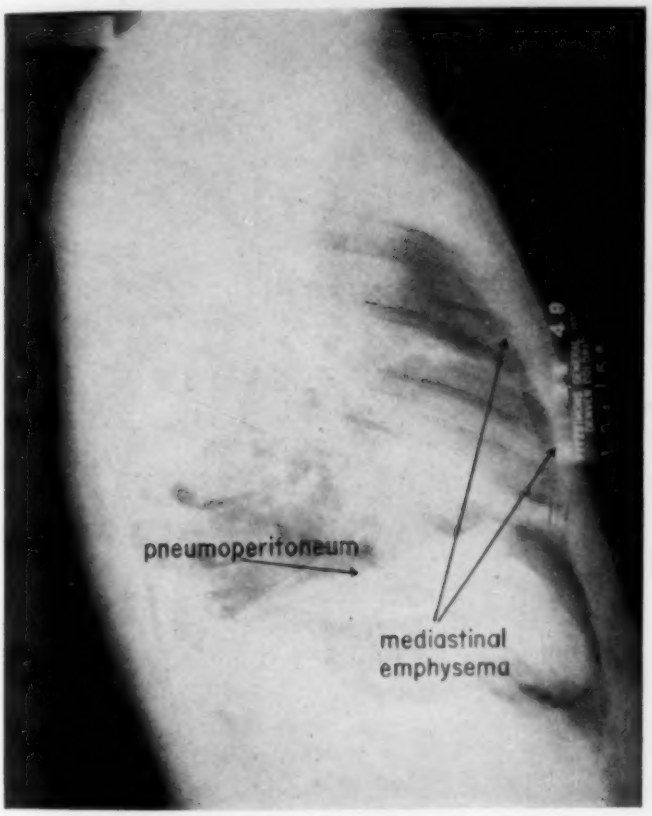

FIG. 6. Case 7.

creased intraalveolar pressure, and these two elements coöperate to produce rupture of alveolar bases. Hyperinflation of the alveoli may arise from forceful respiratory efforts against resistance with the glottis closed, or with tracheal insufflation. Under certain circumstances there may be a combination of Factor A and Factor B which heightens the opportunity for air to escape into the perivascular and peribronchial sheaths.[162]

The pathogenesis of mediastinal emphysema secondary to gas from below the diaphragm may be explained by several methods. Gas is pro-

duced in the intestinal tract either by the fermentation of food undergoing chemical decomposition or by gas-forming organisms. Following injury to the intestinal wall, this gas may escape into the surrounding cutaneous tissues and form emphysema. Demarquay [95] postulated that traumatic lesions of the parietal peritoneum associated with perforation or non perforation of the intestinal canal allowed gas to diffuse into the subcutaneous tissues, but he suggested no definite route. Erichsen [97] stated that in his

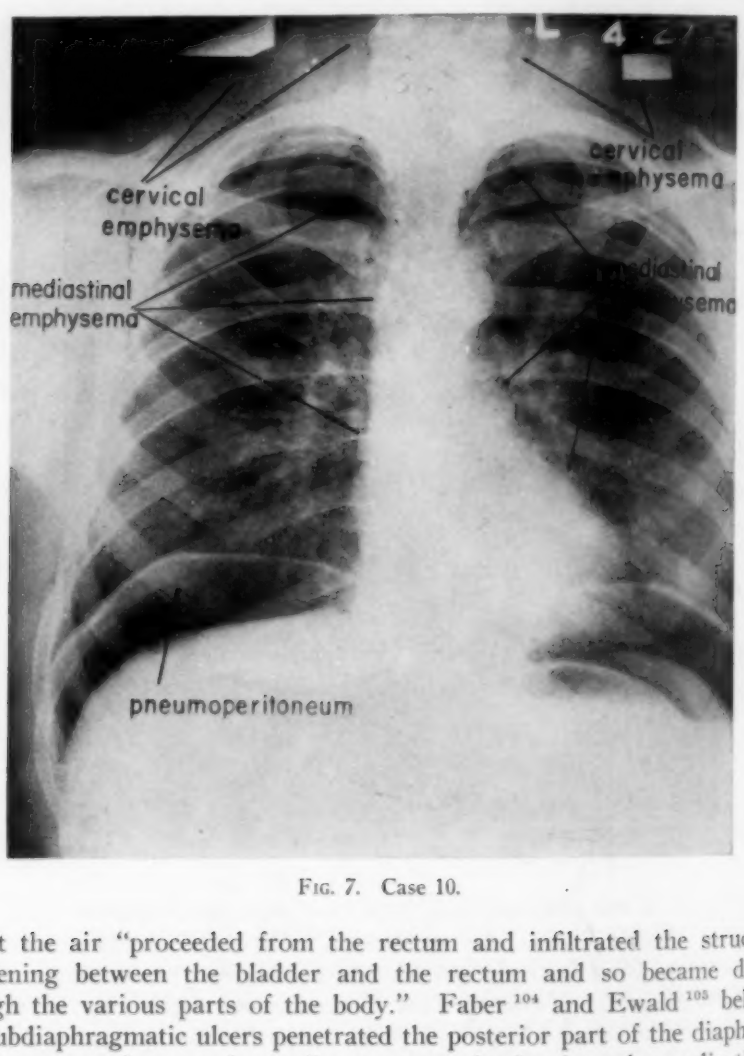

FIG. 7. Case 10.

patient the air "proceeded from the rectum and infiltrated the structures intervening between the bladder and the rectum and so became diffuse through the various parts of the body." Faber [104] and Ewald [105] believed that subdiaphragmatic ulcers penetrated the posterior part of the diaphragm near its center, thus opening a direct communication into the mediastinum. Rupture of the intestinal wall by compressed air insufflation [106 to 111] split the peritoneum, and the free gas escaping into the retroperitoneal space forced

its way either up the esophageal and aortic structures into the mediastinum, or downward into the tissues of the scrotum, thighs and anterior abdominal wall. In Speed's [112] patient the rectum, containing considerable gas in association with a tight sphincter and a contracted abdominal wall above, was punctured from violent compression. The injury was extraperitoneal because no symptoms of peritonitis were present; instead, generalized emphysema developed from the toes to the clavicle. At operation a "small valvelike opening from the rectum was found permitting gas to infiltrate the subcutaneous tissues."

Vigyázó [113] found in his patient that the margin of the serosa overhung the duodenal perforation. The serosa acted as a valve and kept the air from the duodenum out of the abdominal cavity, forcing it instead directly into the subcutaneous sheaths via the swollen serosa. An alternate route, he stated, "may be the subserous migration of gas either along the hepatoduodenal and round ligaments or into the retroperitoneal tissues, and thence around the flanks to the anterior abdominal wall." Podlaha [114] injected hydrogen peroxide into the subserous tissues of dogs and cadavers and discovered that injections in the region of the pylorus diffused along the hepatoduodenal and round ligament of the liver to the umbilicus. When instillations were made near the cardia, the material accompanied the phrenico-esophageal ligament, the aorta and the esophagus into the posterior mediastinum. It is interesting to note that in the patient described by McCorkle and Stevenson [101] extensive pneumoperitoneum developed, accompanied by mediastinal and subcutaneous emphysema, but at operation there was no demonstrable emphysema in either the ligamentous structures or the retroperitoneal space. They concluded that a satisfactory explanation is not yet available for the occurrence of mediastinal and subcutaneous emphysema accompanying perforated intestinal ulcers. These observers think that diffusion through the parietal peritoneum is feasible only when this membrane is damaged by inflammation and pneumoperitoneum is extensive and under pressure. They also believe that gas diffusion along either the peritoneal covered ligamental structures about the stomach and duodenum, or into the retroperitoneal tissues, requires precise mechanical conditions at the site of injury, such as a valvelike flap or an irregular linear perforation which will allow "the pumping of gas" into the subserous tissues from the stomach. Brown and Fine [115] believed that in their patient, who received a double contrast enema, the insertion of the nozzle was not forceful enough to penetrate the mucous membrane of the rectum and no evidence of a fistulous tract was found. The nozzle may have reached beyond the rectal wall, permitting air to accumulate in the retroperitoneal space surrounding the kidneys and extend up through the diaphragm to the mediastinum. Although no lesion was found in the rectal mucosa by which air escaped, there must have been a tear in the alimentary tract at some point. In commenting on Smith's [117] observations, Macklin [102] contends that the

air traveled up through the connective tissue about the aortic and esophageal hiatuses over the same route which is followed when air in the mediastinum migrates down into the retroperitoneal space. According to Hamman,[69] the injection of air into the perirenal tissues to facilitate roentgenologic study of the kidneys has resulted in the formation of mediastinal emphysema.

Banyai and Jurgens [149, 150] are of the opinion that the sudden increase in the intraperitoneal pressure in the subdiaphragmatic area allows injected

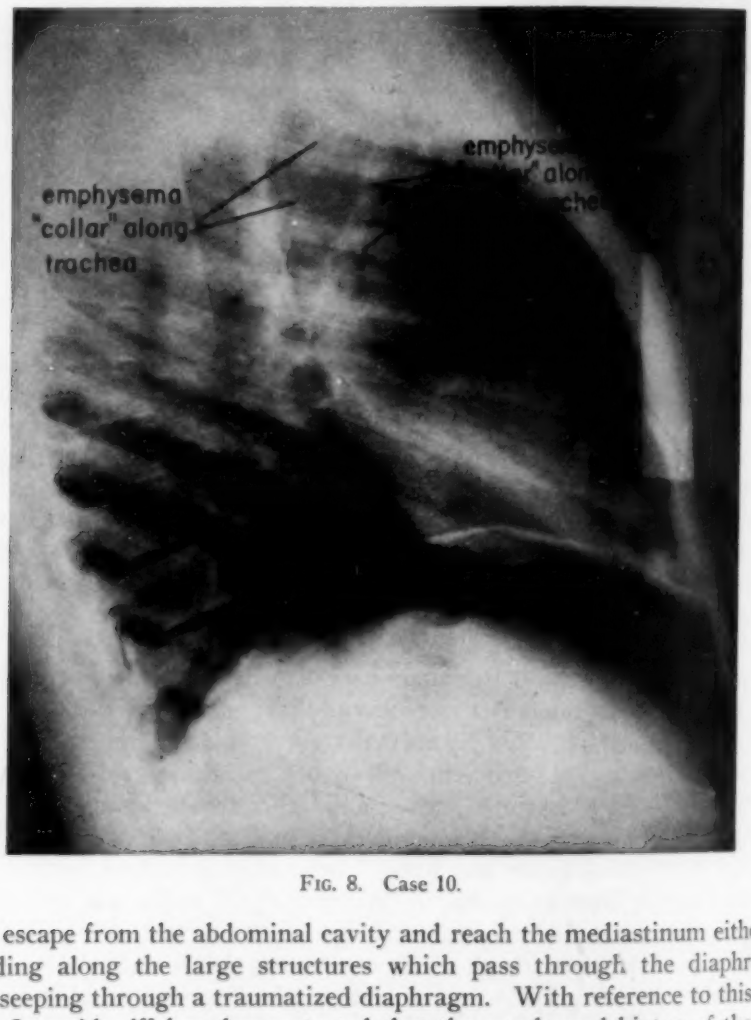

FIG. 8. Case 10.

air to escape from the abdominal cavity and reach the mediastinum either by spreading along the large structures which pass through the diaphragm, or by seeping through a traumatized diaphragm. With reference to this first route, Joannides [163] has demonstrated that the esophageal hiatus of the diaphragm consists of a small inverted triangle, the sides of which are joined together by the fibrous tissue. Under increased pressure from either above or below, air easily finds its way through this opening. In describing the

aortic hiatus, Gray [164] states that "strictly speaking it is not an aperture in the diaphragm, but an osseoaponeurotic opening between it and the vertebral column and therefore it lies behind the diaphragm." Since these hiatuses lie in the retroperitoneal area, the pathway taken by the peritoneal air to reach this space is not obvious. The other method suggested by Banyai and Jurgens may occur if pneumoperitoneum is administered by a subcostal route. The air migrating through the peripheral portion of the diaphragm penetrated by the needle probably elevates the basal parietal pleura and, after dissecting it from the upper surface of the diaphragm, infiltrates the mediastinum.

IV. Clinical Picture

The degree of intramediastinal pressure determines the nature and severity of symptoms which accompany mediastinal emphysema. Jehn and Nissen [157] injected air directly into the mediastinum of experimental animals and demonstrated that no symptoms appeared until the intramediastinal pressure reached zero. As the pressure increased, the effects were similar to those produced by pericardial tamponade. Respiration became rapid and shallow, and was followed by a drop in blood pressure. Since elevations in pressure in a closed thorax can occur only by compression of other intrathoracic structures, the elastic, easily compressed systemic and pulmonary venous walls are the first to be affected. Compression of the systemic veins obstructs the flow of blood into the right heart, while collapse of the pulmonary vessels hinders the return flow into the left ventricle; thus peripheral and pulmonary congestion develops. The bubbles of air press upon the vessel walls and occlude their lumina, producing venous stasis with cyanosis —"the air block" of Macklin.[162] Respiration becomes embarrassed because air which has leaked into the interlobular connective tissues splints pulmonic action and forms a voluminous, rigid lung locked in the position of inspiration, thus producing the dyspnea to which Macklin refers as "air lock." Ballon and Francis [165] demonstrated these effects experimentally by placing in the mediastinum a rubber balloon into which air could be injected or from which it could be withdrawn at will. When air was instilled, a marked drop in blood pressure and a decrease in respiratory amplitude resulted; when air was removed, the blood pressure and respiratory rate quickly returned to normal. They also showed that the direct effect of compression on the trachea, bronchi, and even the lungs was only a minor factor in causing dyspnea.

The ease with which entrapped air leaves the mediastinum is important because this alleviates distress in the mediastinal circulation. The development of palpable emphysema in the axillae, face, neck, supraclavicular fossae and anterior chest wall is a safety factor which diminishes intramediastinal pressure. Similarly, extension of the mediastinal air to produce a simple pneumothorax, retropneumoperitoneum, pneumoperitoneum or scrotal em-

physema relieves compressed mediastinal structures. Pneumothorax, however, may add to respiratory embarrassment if a tension mechanism develops. When the air cannot escape and the pressures continue to rise, then mediastinal emphysema becomes threatening to life.[159, 162]

These findings were corroborated by Torrey and Grosh,[25] who observed acute pulmonary emphysema during an epidemic of acute influenzal pneumonia at an army camp. They stated, "When in apparent respiratory extremis, frequently a patient would begin to complain of pains, substernal and in the jugular fossae, and crepitation would be noted in the subcutaneous tissue at the root of the neck, and immediate marked subjective relief was apparent, rapidly followed by noticeable improvement in respiration and a striking decrease in cyanosis and jugular distention. Cutaneous emphysema soon became diffuse spreading down the trunk to the pubes, first appearing along the sheaths of the cutaneous veins. As the intrathoracic pressure was thus relieved these apparently moribund patients often went on to recovery."

One of the outstanding features encountered in the clinical picture of mediastinal emphysema is pain in the chest. This pain appears suddenly and may be described as sharp, stabbing, knifelike or squeezing, and of such intensity that myocardial infarction is frequently suspected.[67, 68, 71, 88, 92] In many respects it closely simulates the pain of angina pectoris. The similarity in radiation of angina pectoris and mediastinal emphysema has been attributed to transmission over the same nerves. Macklin [159, 162] has suggested that deposits of air in the mediastinum may indent the coronary arteries and impede the blood supply of the heart, while Scott [71] believes that the anginal pain is caused by streching of the investment of the aorta. The pain is made worse by respiration and, in these respects, simulates pleurisy or pleurodynia. Hyperesthesia of the skin over the precordium has also been noted.[82, 169] Its duration varies from several minutes to hours or days before it gradually disappears. The development of channels for escape of air not only decreases cyanosis and dyspnea but also diminishes the severity of the pain. Its location varies, but usual sites are the precordial, substernal, axillary, anterior and posterior portions of the chest, and midscapular regions. It may radiate to the neck, shoulder, left arm, and down the back.

Other symptoms are anxiety, profuse perspiration, palpitation, dysarthria, and pain on turning the neck. Symptoms of an acute abdominal condition have been simulated by the pressure of air in either the retrosternal spaces or the peritoneal cavity.[166 to 169] Müller's [5] patient was operated upon for the supposed rupture of a gastric ulcer which was not found. This abdominal pain may be due to a downward pressure of the dome of the diaphragm caused by high intrapleural pressures as demonstrated experimentally by Macklin.[160] It has also been explained as referred from a pneumothorax, "but there would seem to be enough pull on the ureters, when the perirenal tissues are distended, to permit the interpretation that this pain is local in origin and not referred." [162]

Another characteristic of mediastinal emphysema is the sound of mediastinal crepitation produced by the heart's contracting against bubbles of air which lie between the parietal pericardium and parietal mediastinal pleura. Laennec referred to this adventitious sound as "a dry crepitant rhonchus with large bubbles." Faber [104] and Müller [5] called it "a low pitched crackling râle accompanying the heart sounds." It is best heard during systole, may be evident during diastole, differs from any other sound audible over the heart, and once heard is never again confused. Mediastinal crepitation has been variously described as crackling, bubbling, popping, rattling, crunching, grinding, rasping and snapping. The sound has been compared to the crackling of cellophane, the sticky popping of noisly chewed gum, the sound heard when one walks in dry crisp snow on a quiet day, the wrinkling of newspaper, the squeaking of a leather saddle, the rattling of dry peas on a taut canvas, the cooing of doves or the rubbing together of distended balloons.[66 to 93] This sound is best heard when the patient lies in the left lateral recumbent position, and it may disappear in the right lateral recumbent position or with the patient erect and leaning forward. It varies with respiration and may disappear during inspiration. This crunching may be sensed by the patient, frequently is audible to him, and occasionally is loud enough to be heard by others at a distance of several feet from the patient's bedside. Laennec stated that "patients are sometimes sensitive of a kind of crackling in the part affected." Patients have referred to this sensation as a "crunching, crackling sound like small chicken bones being crushed," [75] "like bubbles of gas crunching in my chest,"[77] "as if gears were grinding together in my chest," [84] "like water dripping on a shelf," [89] "like tissue paper crackling." [93] When the leakage of air is insufficient to infiltrate the anterior mediastinum or the air bubbles are not at a level in the mediastinum at which they can be pressed upon by the beating heart, these crepitant sounds may not be heard.[162]

The sound of mediastinal crepitation may be mistaken for a pericardial or pleuropericardial friction rub. It is also to be differentiated from "pericardial knock," which may be heard either after trauma or spontaneously. During World War I, Rees and Hughes [44] heard "tapping sounds over the cardiac area in patients wounded in the left chest. These sounds were synchronous with the heart beat and in some instances could be heard several paces from the chest. Sometimes the patients were aware of the sounds." Smith [170] described this sound as "in the nature of a click which may be compared to that heard in the ear piece of the telephone when the lever is moved up and down. The usual disappearance after a short period and the absence of severe symptoms suggest that it may be due to air in the interstitial connective tissue of the lung which is struck upon by the beats of the heart." Greene [13] thought this knocking simulated that heard "coming from the engine of a motor car during a hard pull." He believed it originated from the heart's striking an emphysematous bleb on the median

aspect of a partially collapsed left lung or striking the diaphragm over gas bubbles in the splenic flexure of the colon. Lister [171] stated that the sound was analogous to those heard in estimating blood pressure, and that it originated in a left pulmonary artery obstructed at the hilus by the collapsed left lung. Scadding and Wood [172] described this knock as arising from forcible separation of the visceral and parietal pleura during cardiac systole.

Additional diagnostic criteria of mediastinal air are diminution of the area of cardiac dullness and the presence of subcutaneous emphysema, often accompanied by pneumothorax, retropneumoperitoneum, pneumoperitoneum or scrotal emphysema. Müller [5] recorded the obliteration of cardiac dullness and its replacement by hyperresonance. Jehn and Nissen [157] explained that mediastinal air displaces the heart downward and posteriorly so that heart sounds are distant and the percussion note is tympanitic.

No constitutional sign usually accompanies this syndrome. The temperature, pulse, respiratory rate and blood pressure are not significantly altered.

V. Differential Diagnosis

Any condition characterized by pain in the chest, principally angina pectoris, myocardial infarction, pericarditis, pleuritis, pleurodynia, dissecting aneurysm, pulmonary embolus, spontaneous pneumothorax, broken rib, mediastinitis or a ruptured abdominal viscus, should be considered in the differential diagnosis of mediastinal emphysema. These diseases can be readily differentiated because mediastinal emphysema usually occurs without the general clinical picture of shock, fever, leukocytosis, elevated sedimentation rate or significant electrocardiographic changes; with the production of mediastinal crepitation, diminished cardiac dullness, and roentgenographic evidence of mediastinal air; and with the appearance of palpable emphysema in the subcutaneous tissues, and accompanied sometimes by spontaneous pneumothorax, pneumoperitoneum or scrotal emphysema.

In addition, the differential diagnosis should include pneumopericardium, i.e., gas in the pericardial sac (table 1). Pneumopericardium may occur secondary to spontaneous gas formation from infected fluid, perforation of the pericardium by erosion from a disease process, trauma to an adjacent structure, irradiation necrosis, and deliberate or accidental introduction during pericardiocentesis.[192] While the occurrence of spontaneous mediastinal emphysema is unusual, pneumopericardium of known or unknown etiology is found even less frequently. Schrötter had never seen a case of pneumopericardium during his 35 years at the Vienna City Hospital, nor had Skoda, his predecessor, while Müller by "lucky chance" studied three cases clinically.[174, 183] Shakelford,[175] in 1931, after an exhaustive study of the literature, was able to collect 76 cases which had been recorded during the previous 100 years, and since then, only 10 additional reports have appeared.[176]

Although Shakelford's review contained two cases of indefinite etiology, he concluded that they were produced by inflammatory processes and hence

TABLE I

Differential Diagnosis of Mediastinal Emphysema and Pneumopericardium

Diagnostic Feature	Mediastinal Emphysema	Pneumopericardium
ETIOLOGY	1. Following trauma to face or neck. 2. Through a perforation of the trachea, bronchus or esophagus into the mediastinum. 3. From retroperitoneal space. 4. From interstitial tissues of the lung.	1. Spontaneous gas formation from infected fluid. 2. Perforation by erosion from a disease process. 3. Trauma to an adjacent structure. 4. Deliberate or accidental introduction during pericardicentesis.
SYMPTOMS	Pain. Location: Inconstant; precordial, substernal, axillary, anterior or posterior chest. Type: Stabbing, knifelike. Patient aware of sensation, with anxiety, palpitation, dysphagia, pain in turning neck, dyspnea or cyanosis.	Precordial discomfort; pain, dyspnea, syncope, weakness, shock.
PHYSICAL SIGNS Inspection	Face and neck have bulging appearance in extreme cases.	Precordial bulge. Disappearance of apex beat with patient recumbent.
Palpation	Palpable emphysema in subcutaneous tissues.	Not significant.
Percussion	Diminished cardiac dullness or hyperresonance over sternum and precordium with patient recumbent. May disappear with patient upright and leaning forward.	High-pitched tympanitic note over precordium with patient recumbent. With patient upright, tympany over upper and dullness over lower part of precordium. Tympanitic areas shift with change in posture.
Auscultation	Sound synchronous with heart beat. Crunching, crackling, popping, snapping, clicking, rattling. Simulates cooing of doves; popping of noisily chewed gum; walking on crisp, dry snow; rubbing together of distended balloons; squeaking of a leather saddle; crunching of cellophane; wrinkling of newspapers (Hamman's sign).	Sound synchronous with heart beat. Splashing, churning sound over the precordial area. Mill-wheel murmur, crackpot sound or metallic tinkling. "bruit de moulin" "bruit de la roue hydralique" "bruit de pot fele"
ROENTGEN EXAMINATION Fluoroscopy	Cardiac pulsations not significantly altered.	Bizarre type of cardiac pulsation with markedly increased amplitude. The heart mass swings and rotates considerably and shows hammerlike, vertical movements. The interposition of air frees the heart from the "reining effect" of the pericardial sac.
Roentgenogram	Area of increased radiance delineated by a distinct white line which runs parallel to one or both heart borders. "Air streaks" in the cervical or other soft tissues.	Clear, gas-filled space about the cardiac shadow surrounded by a narrow band of pericardium with the shadow of a fluid level in the inferior portion of the sac.
ELECTROCARDIOGRAM	Inconstant deviations. Low voltage: S-T segment elevations, T-wave changes.	Low voltage: S-T segment elevations, T-wave changes.
CONSTITUTIONAL SIGNS	None present.	If infection is present, temperature, pulse and respiration are elevated; otherwise, no significant alterations.

were not examples of primary pneumopericardium. Mölnar [178] had previously cited a case of his own and also those of Ljungdahl [179] and Saupé,[180] in which pneumopericardium accompanied therapeutic pneumothorax, but Shakelford believed these patients had tuberculous pericarditis. Hamman [68] also questioned the diagnoses of pneumopericardium in these latter instances, maintaining that the clinical histories and physical findings were, instead, characteristic of mediastinal emphysema. In a patient of Lundie's,[181] pneumopericardium was apparently caused also by a pericarditis, while in Cowan's patient,[182] a gas producing bacillus was probably the etiologic agent.

Buzni [183] reported the case of a patient with tuberculosis in whom bilateral pneumothorax with a "non-infected pneumopericardium" was demonstrated at autopsy. He suggested that "endopleural pressure produced by a left spontaneous pneumothorax ruptured the pericardium in the region of the pleuro-mediastinal union thus allowing air to enter the cardiac capsule."

Of the 10 cases reported since 1931, four were of obscure origin.[177, 184 to 186] Ghimus and Popescu's [184] patient was a five year old child who developed pneumopericardium following a thoracotomy for empyema. Physical and roentgenographic findings confirmed the diagnosis of pneumopericardium. These writers believed that a small opening in the mediastinal pleura permitted air to pass from the pneumothorax space into the pericardial sac, but the exact route was not clear. They implied that this was the only case of "pure pneumopericardium" ever recorded.

Gilbert [185] reported the case of a 20 year old farm hand (with no history of cancer or tuberculosis) who noted slight precordial discomfort while lifting bales of hay from the ground to the back of a truck. When walking home shortly thereafter, he became aware of a peculiar noise in his chest and an "unusual action" of his heart. At the dinner table the family commented on the clarity of these peculiar sounds, which increased in volume but were not painful or uncomfortable. Physical examination revealed a bradycardia and bizarre, clinking metallic noises occupying both systole and diastole, unrelated to respiration and audible over the entire examining room. Roentgenograms, initially read as negative, later revealed a double cardiac outline compatible with air in the pericardial sac. Gilbert postulated that this patient might have developed a pleuropericardial adhesion following a severe attack of pneumonia nine years previously. "It is conceivable that this old pleuropericardial adhesion was torn during the muscular and respiratory effort of lifting bales of hay to a height above his head. Instead of developing a spontaneous pneumothorax, the tear was directly into the pericardial sac. Ruptured pulmonary alveoli may have formed the vesicles which tore through the old adhesions, producing pneumopericardium instead of pneumothorax."

In Lages Netto's [177] patient, pneumopericardium was produced secondary to a lung abscess at the base of the right lower lobe. We do not have access to the case of pneumopericardium described by Levy and Cantor.[186]

Graebner,[89] in describing the treatment of five patients with acute obstructive laryngitis, noted that two developed pneumopericardium and two developed mediastinal emphysema following tracheotomy, while the fifth developed mediastinal emphysema prior to the operation. He was able to differentiate the two conditions without difficulty by clinical and roentgenographic studies. Both of the patients with pneumopericardium recovered, hence the problem of tracing the pathway of the air into the pericardial sac remained unsolved. He concluded, however, that a mechanism similar to that described by the Macklins in producing experimental mediastinal em-

physema prevailed here. The air, he stated, probably migrated along the perivascular sheaths into the mediastinum and then gained entrance into the pericardial sac at the point where the pericardium is deflected along the large vessels. Replying to an inquiry relative to these cases, Dr. Macklin stated he had never seen evidence of pneumopericardium in any of his experimental animals. A careful search of the literature failed to disclose any point where the air could penetrate the pericardial sac, nor has this condition ever been produced experimentally in a living animal.

Trimble [187] cited the example of the development of spontaneous pneumopericardium in a patient who had received alternating bilateral pneumothorax. The disease had become arrested and both lungs were reëxpanded, the right lung for five and one-half years and the left for two years. While driving to work, the patient felt a peculiar substernal ache, followed shortly thereafter by "gurgling sensations" accompanying each heart beat. Physical and roentgenographic examinations confirmed the diagnosis of pneumopericardium. There was no fluid in the pleural cavity, nor was air demonstrable in either the mediastinum or the subcutaneus tissues. It was suggested that tubercles involving the pleura and pericardial sac may have eroded these membranes, with the consequent entrance of air into the pericardial sac.

The symptoms of pneumopericardium, in contrast to the physical signs, are not characteristic. While attacks of sudden dyspnea and sharp precordial pain may be present, the symptoms depend on the individual condition, such as sepsis occurring with purulent effusion, or cyanosis occurring with massive amounts of gas.[188] The physical signs are distinctive. On percussion, tympany is present over the precordial area, shifting with change in position. Auscultation reveals a splashing, gurgling, churning sound synchronous with the heart beat.[189] One may also hear a metallic tinkle or metallic rub which is accentuated by shaking the patient. Hydropneumothorax and giant pulmonary cavity can be distinguished easily by the absence of the characteristic heart sounds and the definite changes in the breath and voice sounds which distinguish the two latter conditions. However, differentiating pneumopericardium from the presence of gas in the mediastinum or pericardial tissues is difficult, and the danger of confusing these two complications was specifically noted by both Saupé [180] and Petersen.[190] Fluoroscopy reveals a bizarre type of cardiac pulsation with a markedly increased amplitude, and the roentgenogram shows a clear gas filled space about the cardiac shadow surrounded by a narrow band of pericardium, with the shadow of a fluid level in the inferior portion of the sac.[188, 192] Mayer [191] reported difficulty in distinguishing mediastinal emphysema from pneumopericardium by roentgenographic study. In mediastinal emphysema, the gas in the tissues appears as small areas of increased radiability separated by fine shadows. In pneumopericardium, the area of gas is homogeneous and the pericardium is sharply defined.[188]

VI. Laboratory Findings

I. *Roentgenographic Studies:* These studies are invaluable aids in establishing the diagnosis of mediastinal emphysema. If mediastinal crepitation is not audible, examination in the lateral and oblique positions may be decisive in revealing the presence of air behind or in front of the heart and in the superior mediastinum above the heart.[162] On the roentgenogram one notes an area of increased lucency sharply delineated by a distinct white line which runs parallel to one or both borders of the heart. This line represents the outer edge of the mediastinum as the lung is pushed out from behind the cardiac shadow.[82] However, it should be borne in mind that occasionally the normal mediastinal border is visible in adults on deep inspiration. In the cervical tissues and other soft tissues, subcutaneous emphysema appears as "streaks" of increased radiolucency in the fascial planes.

II. *Blood Studies:* Blood counts are not significantly changed, although initially some leukocytoses may occur. The sedimentation rates are not elevated.

III. *Electrocardiographic Studies:* No constant changes in the pattern of the electrocardiogram are observed. Deviations in the electrical axis, low voltage, changes in the T wave and elevation of the ST segment have been reported.[33, 67, 72, 73, 88, 91, 195] The exact mechanisms producing these conduction disturbances are controversial, since pneumothorax alone may cause similar abnormalities in the electrocardiographic pattern.[193, 194, 196, 197, 198] Littman [195] explains these changes in the electrocardiogram as the result of air between the heart and the exploring electrode interfering with conduction. Master, Dack, et al.[193] stated that these alterations are probably due to rotation and displacement of the heart caused by air in the pleural cavity. Other observers [73, 162] suggest that mediastinal air may indent the coronary arteries and thus interfere with the blood supply of the heart. Miller [88] considers temporary functional coronary insufficiency the result of stasis which induces resistance to coronary emptying.

IV. *Phonocardiographic Studies:* Phonocardiographic studies illustrate that the peculiar sounds produced by mediastinal crepitation are synchronous with each cardiac impulse and occur regularly with each cardiac contraction.[198]

VII. Treatment

The primary objective in the treatment of mediastinal emphysema is immediate relief of the elevated intramediastinal pressure. Therapy must therefore be designed to eliminate the production of air and to provide an outlet for the air already accumulated. To control the source of air, rents in the lungs, bronchi or other viscera must be ligated and sucking wounds closed air tight.[38] The means of ruling out the presence of a simple or tension pneumothorax are extremely important. If only a simple pneumothorax has resulted, dyspnea may be relieved by merely decompressing the

lung. However, if a tension mechanism has developed, diversion of the intrapleural air to the exterior must be accomplished by the insertion of a valve drain.[45, 200] By using this apparatus, the air which enters the pleural cavity during expiration is expelled through the water seal during inspiration and is thus prevented from entering the mediastinal and subcutaneous tissues. If the intramediastinal pressure becomes markedly increased, accompanied by dyspnea, cyanosis and changes in blood pressure, then the suprasternal notch should be immediately incised and the air drawn out by means of an inverted funnel attached to an electric suction machine.[199] A hard rubber catheter may be inserted from the jugulum into the mediastinum, and trocar needles may be placed in subcutaneous air pockets to afford adequate channels for escape of the air.[102] Additional incisions may be made in the skin of the chest wall, at the base of the neck and in the clavicular fossae, to facilitate the release of the entrapped gas.[32] If mediastinal emphysema develops after such operative procedures in the neck as thyroidectomy, a cold wet pack placed substernally may prevent further entrance of the air into the mediastinum.[51] Continuous inhalation of oxygen by means of a mask or a nasal catheter may be employed. Collections of "air" beneath the skin and in the mediastinal space consist almost entirely of nitrogen. With the patient breathing 100 per cent oxygen, the nitrogen concentration is diluted by the oxygen, which diffuses more readily through the tissues, thereby reducing the volume of "air" in the interstitial spaces. In addition, the pure oxygen aids in combating anoxia. Pain should be relieved, because the splinting action of the thorax favors progression of the emphysema. If cyanosis becomes extreme, venesection may be indicated. Bed-rest is mandatory in patients with spontaneous pneumothorax because of the possibility of recurrence. The individual should remain as quiet as possible, since coughing, straining or exercise may expel more air from the lungs into the interstitial tissues. Other supportive measures consist of analgesics and sedation to allay apprehension. Assurance should be given the patient that he has no serious pulmonary or cardiac illness. If an associated upper respiratory infection is present, antibiotics may be desirable to reduce the possibility of a dangerous mediastinal infection.

VIII. Discussion

The occurrence of mediastinal emphysema with therapeutic pneumoperitoneum does not lend itself to the relatively simple explanation which is advanced for spontaneous emphysema that occurs in the chest.

An explanation is first necessary for the mechanism which permits air to leave the closed peritoneal space. If trauma to the parietal peritoneum is a major factor, then this type of mediastinal emphysema should have a higher incidence. At Fitzsimons General Hospital during 1947 and 1948, pneumoperitoneum was induced in 225 patients and a total of 8,960 refills was administered with no record that this condition ever developed.

The suggested technic of induction is to place the patient flat on his back and, using strict asepsis, to sterilize the periumbilical area with merthiolate. The skin and various layers of the abdominal wall are slowly infiltrated with novocaine. The site of choice in selecting the point of entry is through the left rectus muscle, two fingerbreadths to the left and below the umbilicus. The skin is first punctured with a dull needle and through this point a Fisher needle is inserted. When the needle pierces the peritoneum, an oscillating positive pressure of 6 to 10 cm. of water immediately registers and the air flows freely. If the point of the needle fails to reach the abdominal cavity but lies instead in the surrounding tissues, the air flows slowly, non-oscillating pressures of 15 to 30 cm. of water rapidly develop, and the patient complains of discomfort at the site of the needle.

In reviewing the literature for this study, as stated previously, only 15 instances have been recorded of mediastinal emphysema occurring with pneumoperitoneum. However, the number of patients in the different series receiving pneumoperitoneum has varied from 16 to 710; the duration of observation has ranged from nine months to 10 years, and the number of peritoneal refills has varied from 200 to 13,000. Therefore, the paucity of this complication precludes indicting peritoneal puncture per se as an etiologic agent.

Simple diffusion, either directly through the parietal peritoneum or through peritoneal covered ligamentous structures about the stomach and duodenum, may occur when a viscus ruptures and the consequent inflammation renders this membrane more permeable. In the absence of such conditions, it is difficult to reconcile diffusion with aseptically instilled air.

Congenital or acquired peritoneal defects may afford an opportunity for air to escape from the peritoneal cavity. The general pressure within the abdomen tends to equal that of the atmosphere, but a portion of the negative intrapleural pressure is transmitted to the subdiaphragmatic region. When air is instilled into the abdominal cavity, the combined pulling force of the intrapleural negative pressure and the intraperitoneally injected air might exaggerate any abnormality in the peritoneal covering. However, if this method is tenable, one is led to inquire why mediastinal emphysema does not recur with subsequent peritoneal air instillations.

One should always consider the possibility that a patient with pneumoperitoneum may develop interstitial emphysema from pulmonary causes, with resulting mediastinal emphysema which is totally unrelated to the presence of air administered below the diaphragm. With reference to this study, cases 2 and 8 demonstrate this possibility. In these patients, mediastinal emphysema probably developed secondary to conditions prevailing in the chest and bore no relationship to the injected air in the abdominal space.

In the remaining cases, no definite mechanism is apparent to adequately explain the escape of air from a closed peritoneal cavity.

Another problem in addition to ascertaining how the peritoneal air

escapes is determining the route taken by the released air to reach the mediastinum. Most writers agree that the free air accompanies the aorta and esophagus, as these structures pass through the diaphragm. To accomplish this, therefore, the air must first occupy the retroperitoneal tissues, but the path by which it arrives here is conjectural. However, from the retroperitoneal area the air may travel either up or down in a manner similar to gas injected retroperitoneally for roentgenologic studies of the kidney. The course up into the mediastinum is merely the reverse of that taken by supradiaphragmatic air as it passes down through the various hiatuses. The route from the retroperitoneal tissues into the scrotum and thigh is identical to that of any interstitial air which dissects down the fascial planes to afford relief of increased pressure from above.

When the subcostal approach was used in establishing pneumoperitoneum, it was possible for air to travel into the mediastinum by seeping through the peripheral portion of a diaphragm traumatized by the needle puncture. Since this technic has been virtually abandoned, it is no longer an important etiologic factor.

An experimental study, using nebulized methylene blue intraperitoneally to delineate the course which released air pursues to reach the retroperitoneal space and the mediastinum, may help solve this problem.

The clinical picture of mediastinal emphysema occurring with pneumoperitoneum differs somewhat from that encountered with spontaneous mediastinal emphysema developing in the chest. The primary subjective feelings of the patients in the former condition consist of tightness in the neck, pain on twisting the neck, discomfort in swallowing and difficulty in talking. Thoracic pain is seldom present but, when it appears, is mild in character. Mediastinal crepitation is audible in most instances with the patient either lying down or sitting erect, and the crunching is unrelated to either phase of respiration. Constitutional symptoms are absent. The only significant laboratory findings are the roentgenographic studies. The treatment of mediastinal emphysema occurring with therapeutic pneumoperitoneum is similar to that administered for simple pulmonary mediastinal emphysema. The withdrawal of air from the abdominal cavity may be desirable in some instances but was not necessary in any patient observed in this study.

It is doubtful that spontaneous pneumopericardium accompanying spontaneous mediastinal emphysema ever occurs. The pericardium is a tough membrane, and it is difficult to believe that a simple mechanism such as the rupture of a pulmonary alveolus could easily tear through it. Cadavers have been insufflated with oxygen under the pressure of several atmospheres and the heart carefully examined thereafter under water. In no instance did the air penetrate the durable, inelastic parietal pericardium. One may postulate that fluid developing in association with mediastinal emphysema might produce a splashing noise over the precordial area which could be confused with the sound heard when fluid forms in the pericardial sac.

IX. Summary

1. Mediastinal emphysema may develop from precipitating factors located either above or below the diaphragm.

2. A review of the literature reveals that only 15 cases of mediastinal emphysema occurring with therapeutic pneumoperitoneum have been recorded to date.

3. Ten new cases are reported. In two patients, mediastinal emphysema probably resulted from conditions present in the chest, but in the remaining eight instances, both the method by which the gas escapes from a closed peritoneal space and the route which it takes to reach the mediastinum are obscure.

4. The pathogenesis of this syndrome is discussed.

5. The characteristic features of mediastinal emphysema are precordial pain, dysarthria, dysphagia, subcutaneous emphysema in the neck, scrotum and other soft tissues, diminished cardiac dullness, mediastinal crepitation on cardiac auscultation, roentgenographic evidence of mediastinal air, and the absence of fever, leukocytosis, elevated sedimentation rate and significant electrocardiographic changes.

6. The differential diagnosis between spontaneous mediastinal emphysema and pneumopericardium is noted. It is doubtful that spontaneous pneumopericardium accompanying spontaneous mediastinal emphysema ever occurs.

7. Treatment usually involves only reassurance and symptomatic measures. However, if the intramediastinal pressure becomes excessive, cutaneous incisions in the suprasternal notch and elsewhere must be made to facilitate rapid release of the entrapped air. It is also important to determine whether a simple or a tension pneumothorax exists.

X. Conclusion

Mediastinal emphysema occurring with therapeutic pneumoperitoneum is rarely recorded in medical literature. This complication has probably been unrecognized in many previous instances. Further investigation is required to furnish an explanation for the mechanism which permits the gas to escape from a closed peritoneal cavity, and for the route it takes to reach the mediastinum.

Acknowledgment

The author wishes to thank Dr. James J. Waring, Civilian Consultant in Internal Medicine, Fitzsimons General Hospital, for his valuable suggestions included in this paper. The author acknowledges the assistance of James M. Brown, Major, M.C., Resident in Pathology, Fitzsimons General Hospital, for information obtained from experimental studies which he is conducting on (1) the mode of production of primary pneumopericardium, and (2) mediastinal emphysema occurring with pneumoperitoneum. The author also wishes to thank his associates on the Tuberculosis Division of the Medical Service, the Radiology Service and Miss Myrna A. Barrett, Medical Librarian, Fitzsimons General Hospital, for their assistance in preparing this paper.

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PULMONARY CHANGES RELATED TO CARDIOSPASM *

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PAST medical literature is only sporadically documented with instances of pulmonary findings associated with cardiospasm. Aspiration of esophageal overflow, however, has long been recognized as a source of certain types of pulmonary disease, usually secondary to such causes as esophageal neoplasm, caustic stricture of the esophagus, pulsion diverticulum, esophageal encroachment from extrinsic tumors, foreign body in the esophagus, and postoperative emesis. The source of chronic or recurrent pulmonary disease of unknown origin, however, is seldom associated with the well-recognized clinical entity of cardiospasm.[1]

In 1938 Sampson [2] found in the files of Peter Bent Brigham Hospital only one case in which cardiospasm and lung abscess coexisted. In his series of 276 cases of lung abscess at Boston City Hospital, Freedman [3] found none of cardiospasm or other esophageal abnormality, and there were no cases of unexplained origin. Gray and Jankelson [4] in 1944 described two cases of pneumonitis caused by cardiospasm, and emphasized the nocturnal danger of esophageal overflow when reflexes are depressed (especially in debilitated patients). Hawes and Soule [5] in 1945 described two cases of extensive interstitial pulmonary fibrosis associated with cardiospasm and without significant pulmonary signs and symptoms. They considered these roentgen findings the result of pneumonia, due probably to inhalation of esophageal contents. In 1936 Dirkse [6] reviewed in the University of Michigan Hospital Bulletin 159 cases of chronic obstructive lesions of the esophagus, in order to determine any possible etiologic relationship with pulmonary inflammations due to aspiration. In this series, the obstructions in 33 cases were associated with cardiospasm, in 58 with neoplasm, in 42 with diverticulum and in 26 with assorted obstructive lesions. All cases with pulmonary lesions not chronologically related to chronic obstruction of the esophagus, or which were not compatible clinically or by roentgen-ray with an aspiration pneumonitis, were eliminated, as were all postoperative cases. Of the 159 cases, there remained only six in which pneumonitis was directly associated with a preëxisting chronic obstruction of the esophagus, although how many of these six were related to cardiospasm was not stated.

Cardiospasm complicated by basilar pneumonitis was first reported in 1914 by Eisenstein.[7] Since then, five other types of pulmonary changes have been described in relation to cardiospasm: lung abscess, bronchiectasis, pleural effusion, atelectasis and interstitial pulmonary fibrosis. The case

* Received for publication April 10, 1950.
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histories involving these changes often reveal them to be reversible in proportion to the success attained in eliminating the coexisting cardiospasm. It is well to note, however, that pulmonary changes in roentgenologically proved cases of cardiospasm frequently develop insidiously, unheralded by clinical pulmonary symptoms of sufficient magnitude to explain them adequately. Conversely, significantly severe and recurrent pulmonary symptoms may not infrequently play a characteristic part in the course of cardiospasm without the development of any recognizable pulmonary roentgen-ray changes.

To emphasize the significance of pulmonary signs and symptoms related to cardiospasm, a survey was made from University Hospital records, covering a period of slightly more than five and one-half years (January, 1944, to August, 1949), of all roentgenologically proved cases of cardiospasm. Of the 124 cases reviewed, only those were chosen with which signs and symptoms of pulmonary involvement were chronologically and clinically related,

TABLE I

Duration of Cardiospasm Symptoms	Duration of Pulmonary Symptoms	Psychiatric Contributing Factors
3–4 years	1½ years	+
7½ years	7½ years	+!
1½ years	Few days	?
30 years	—	0
9 years	2 months	?
2–3 years	2½ years	+!
10 years	2 years	+
? Many years	Days	+
4 years	4 years	+
20 years	4 months	0
10–12 years	Many years	0
5 years	2–3 months	+

with or without pertinent roentgen findings. Only 12 of the 124 cases (9.6 per cent) fulfilled these criteria. Findings in these cases are outlined in table 1.

The ages of this group of 12 (five of whom were female) ranged from 10 to 65. Each case displayed two or more of the characteristic symptoms of cardiospasm (such as dysphagia, ease of satiation, regurgitation or emesis, epigastric pain or burning, and weight loss). All but one case had pulmonary symptoms significantly related to exacerbations of cardiospasm; the one exception developed otherwise unexplained roentgen-ray evidence of pneumonitis with pleural effusion, which gradually cleared over a long period following frequent esophageal dilatations (table 2).

In only five of the 12 cases was there any roentgen evidence of various types of pulmonary involvement, which included bronchiectasis, pneumonia, atelectasis, lung abscess and pleural effusion. The duration of cardiospasm symptoms ranged widely within the group, from one and one-half to 30 years, and in only three cases did the onset of pulmonary symptoms coincide

TABLE II

Patient	Age	Sex	Symptoms of Cardiospasm					Clinical Evidence of Related Pulmonary Involvement	Roentgen Evidence of Pulmonary Involvement				
			Dysphagia	Regurgitation and/or Emesis	Epigastric Pain or Burning	Weight Loss	Ease of Satiation		Bronchiectasis	Atelectasis	Pneumonia	Pleural Effusion	Lung Abscess
G. B.	31	M	+	+	0	0	0	+	0	0	0	0	0
J. T.*	10	M	+	+	0	+	0	+	+	+	+	0	0
H. P.	25	M	+	+	0	0	0	+	0	0	0	0	0
W. M.	64	M	+	+	+	+	+	0	0	0	+	+	0
H. H.	65	M	+	0	+	+	0	+	0	0	0	0	0
G. McK.*	48	F	+	0	0	+	+	+	0	0	0	0	0
G. W.	38	F	+	+	0	+	0	+	0	0	0	0	0
R. R.	63	M	+	0	+	0	0	+	0	0	+	0	0
F. M.	49	M	+	+	0	+	0	+	0	0	0	0	0
C. S.	60	F	+	0	+	+	+	+	0	0	+	0	+
M. P.	33	F	+	+	0	+	0	+	0	0	0	0	0
C. McD.*	25	F	+	+	0	0	0	+	0	+	0	0	+

* See text.

with the onset of cardiospasm. One patient's symptoms of cardiospasm antedated any pulmonary symptoms by 20 years (table 2).

Fifty per cent of the patients' histories recorded clear-cut evidence of the correlated psychiatric problems which so frequently play a major rôle as predisposing factors in the development and persistence of cardiospasm. Several patients could themselves identify the correlation between emotional upsets, return of cardiospasm symptoms and subsequent pulmonary symptoms (table 2).

Three interesting case histories follow to document this chronologic development of events that often lead to serious pulmonary disease.

CASE REPORTS

Case 1. When this six and one-half year old boy was first seen in the University Hospital in 1943, his history revealed that he had had his first episode of postcibal vomiting at the age of three. His complaint progressed in severity, and when he was four and a half an examination in the Northern Michigan Children's Clinic revealed pallor, weight loss and prompt vomiting even of water. Roentgenograms were said to reveal pneumonitis and early bronchiectasis in the right lower lobe. He received symptomatic treatment, and when first seen at the University Hospital presented the same progressive history and general physical appearance.

He was admitted a few weeks later, and the diagnoses established were malnutrition, cardiospasm with good response to amyl nitrite, bronchiectasis, pneumonitis and, later, atelectasis of the right middle lobe (figure 1). He was not seen again here until re-admitted in March, 1947, with essentially the same symptoms and physical findings, including carious teeth and bilateral cheilosis. There were decreased breath sounds and dullness over the right lung base posteriorly. Laboratory studies revealed only a slightly low hemoglobin of 11.3 gm. The patient was treated with intramuscular and aerosol penicillin, postural drainage and multivitamins for two weeks and was then bronchoscoped. Mucopus was seen to come from the right middle and lower lobe bronchi. Roentgen-ray studies revealed atelectasis and pneumonitis in the right lower lobe and cardiospasm with a huge dilated esophagus that responded moderately to amyl nitrite inhalation. Subsequent esophageal dilatations

for one week lessened somewhat the intensity of his vomiting. Bronchograms obtained then demonstrated, in addition to the atelectasis, mild bronchiectasis within the right lower lobe.

It was soon decided that esophageal dilatations would offer no further improvement, and in June, 1947, the patient underwent an esophagogastrostomy. The postoperative course was stormy, with development of atelectasis of right upper lobe and evidence of upper gastrointestinal bleeding. He received over a period of a month 3,330 c.c. of whole blood and 1,000 c.c. of washed red blood cells because of many

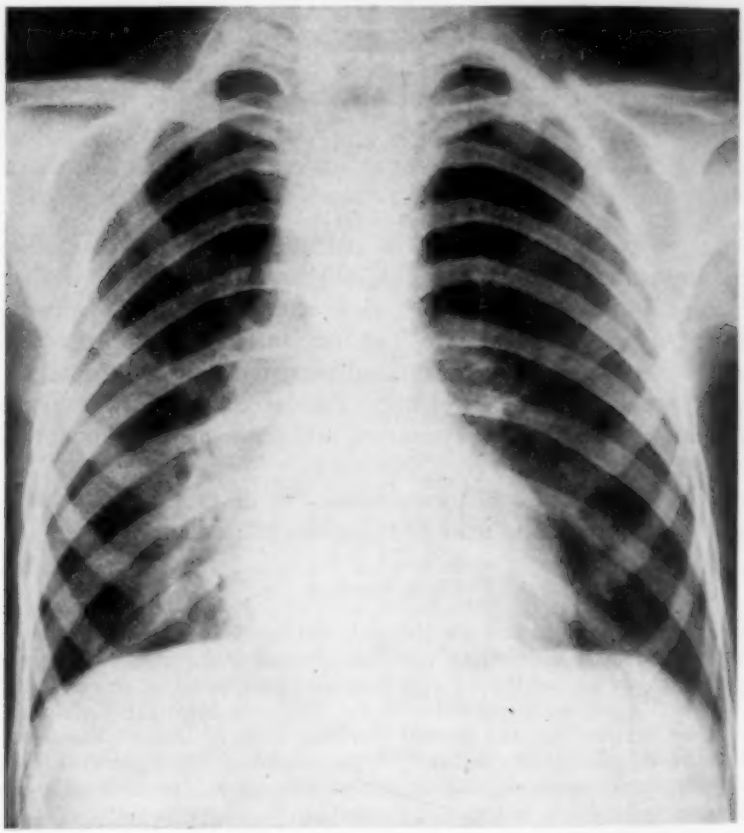

FIG. 1. *Case 1.* J. T. One of the earlier films, revealing the developing area of pneumonitis in the right median lung field.

transfusion reactions. Finally, a left temporary phrenic crush successfully controlled the suspected supradiaphragmatic bleeding site, and his hemoglobin and total serum proteins stabilized.

Psychiatric interviews with the patient revealed a pending divorce in his family, a long dislike for his mother but an idealistic attitude towards his father. He remembered only one emesis when living with his father.

Comment: This case history demonstrates an involved series of events initiated by an underlying cardiospasm in a psychiatrically maladjusted child,

resulting in major operative procedures designed to circumvent the source of his ever-recurrent episodes of pulmonary disease. Earlier, more satisfactory resolution of his disturbed home life, with its expected effect on his cardiospasm, might easily have forestalled this vicious chain of events.

Case 2. This 25 year old Negro woman, first admitted to the Medical Service on December 8, 1948, presented a five year history of dysphagia, ease of satiation, regurgitation and emesis compatible with cardiospasm which had been roentgenologically proved five months earlier by the Otology Department. She had subsequently received several successful esophageal dilatations. She described the onset of a nonproductive cough two months prior to this admission which was soon followed by inspiratory left chest pain and questionable fever. The cough persisted and two weeks before admission became progressively productive of foul-smelling sputum, described as purulent and often bloody. She noted profuse night sweats and weight loss.

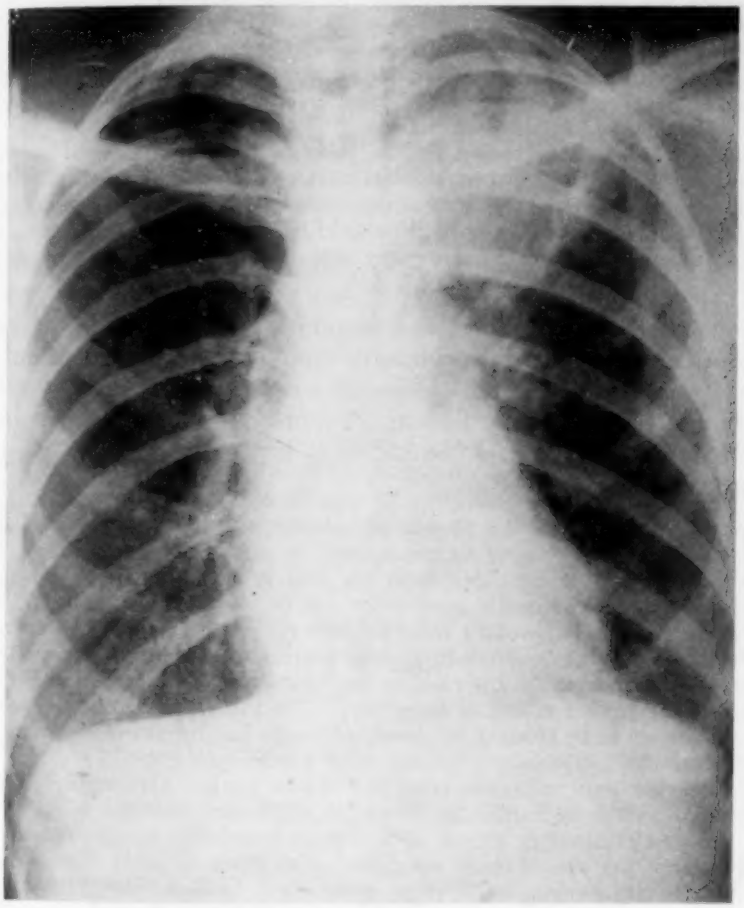

FIG. 2. *Case 2.* C. McD. The diffuse area of increased density in the upper third of the left lung field, containing a central area of rarefaction, is seen in this roentgen-ray.

Physical examination revealed a well developed and well nourished Negro woman with normal temperature, respiration and blood pressure, and a pulse rate of 100. Other than questionable bronchial breath sounds in the left upper lobe, the findings described were noncontributory. Admission laboratory studies revealed no anemia but a leukocytosis of 19,000, with a slight shift to the left in the differential count. Roentgenogram of the chest showed a diffuse increase in density in the upper third of the left lung field, with a 1.5 cm. central area of rarefaction (figure 2), more clearly defined with a Bucky exposure one week later as essentially unchanged.

Diagnoses initially considered, in order of probability, were pulmonary tuberculosis, bronchogenic neoplasm and aspiration abscess. Bronchoscopy was negative except for secretions apparently coming from the left upper lobe bronchial orifice. Four fasting gastric aspirations, four sputum concentrates and two bronchial aspiration specimens were negative on smear and culture for acid-fast bacilli. No malignant cells were identified in bronchial secretions.

The recorded primary reason for the patient's hospitalization was to establish diagnosis, but when she signed out against advice on December 22, 1948, there still was no definite diagnosis. The examiners thought pulmonary tuberculosis most likely, but admitted that acid-fast bacilli should have been found with such a lesion, if it was tuberculous. Penicillin therapy was interrupted by her impromptu departure.

Comment: Although there has been no further follow-up of this patient, review of her developmental pulmonary symptoms, superimposed on an established cardiospasm, would lead one to suspect lung abscess secondary to aspiration of esophageal overflow as the more likely diagnosis, especially in view of the absence of acid-fast bacilli in her pulmonary and gastric secretions.

Case 3. The father of this 46 year old woman was a chronic alcoholic, and her mother was the only sustaining feature in her life. Following her mother's death in February, 1948, the patient experienced her first symptoms of cardiospasm. Very soon thereafter, and continuing once every one or two months, she would develop early morning chills, followed by fever to 102° F., general malaise and aggravation of a previously existing nonproductive cough. On many of these occasions her local physician found fever and moist râles in the lung bases, and administered penicillin, to which she responded in two or three days. The patient noted that the pulmonary symptoms seemed to be brought on shortly after she had increased symptoms of esophageal obstruction, especially if she had eaten a late evening meal.

Although previous roentgenograms had shown marked abnormality in the mucosal pattern and in the caliber of the esophageal lumen, roentgen proof of cardiospasm was first obtained in March, 1948, with fair response to amyl nitrite. At no time was there any demonstrable roentgen-ray evidence of pulmonary disease, and bronchograms taken in August, 1949 were negative. In September, 1949, the patient underwent successful esophageal dilatation, with 90 per cent relief of cardiospasm and pulmonary symptoms. The next month, following a severe emotional upset at home, all symptoms recurred, and it again became necessary to administer penicillin to abort her chest symptoms.

Comment: This history rather definitely records chronologic relationship of exacerbations of acute pulmonary symptoms to emotional situations that predisposed to increase in cardiospasm. At no time thus far, however, have roentgenograms been taken at opportune instances to record roentgen evidence of pulmonary disease.

Conclusions

The foregoing serves to illustrate certain associated events from which the following presumptive conclusions seem justified.

1. Review of the literature, and the significantly large per cent of instances of cardiospasm complicated by pulmonary involvement in this series, indicate the importance of realizing the possibility of this combination of events.

2. Clinical evidence of related pulmonary disease may exist with or without demonstrable roentgen evidence in established cases of cardiospasm.

3. All cases of cardiospasm should be considered potential candidates for development of pulmonary complications resulting from esophageal overflow, even in the absence of pulmonary symptoms.

4. Resolution of related pulmonary disease frequently corresponds to satisfactory treatment of underlying cardiospasm.

5. Well established instances of cardiospasm may present no definite history of pulmonary symptoms, yet demonstrate roentgen-ray evidence of chronic lung disease, probably the result of many subclinical episodes of disease following aspiration of esophageal contents.

Summary

1. Past medical literature surveyed revealed only sporadic reports of pulmonary disease correlated with cardiospasm.

2. Out of 124 cases of cardiospasm reviewed from the records of the University Hospital over a period of five and one-half years, there were 12 (or 9.6 per cent) in which significantly related pulmonary findings were recorded.

3. Three representative case histories are presented.

4. From the presented data certain presumptive conclusions are made.

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CORONARY SCLEROSIS AND PULMONARY HYPERTENSION *

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The cardiac effects of marked deformity of the chest, of chronic bronchitis and of emphysema have been known for many years. New interest in the interrelationship of diseases of the lungs and heart followed the clinical description of acute cor pulmonale and the observed frequency of pulmonary infarction. Cardiac catheterization has recently shown that the postulated pulmonary hypertension actually exists in those diseases of the lungs which bring strain upon the right side of the heart.[1]

Chronic pulmonary heart disease is not uncommon. Spain and Handler [2] have described the findings at autopsy in 60 cases of chronic cor pulmonale unaccompanied by other forms of heart disease; associated contributing factors were anatomic obliteration of the pulmonary vascular bed, fibrosis of the lung, compensatory polycythemia and overfilling of the heart. The authors state that in 26 of the 60 cases an erroneous diagnosis of arteriosclerotic heart disease had been made.

The chronic cor pulmonale is most often observed in persons of middle life or beyond, an age which coincides with the greatest frequency of disease of the coronary arteries. It might be expected that some individuals would show signs of both these disorders, and such is the case. Either process may exert an unfavorable influence upon the other through the production of anoxia and acute changes in the pulmonary circulation.

Mack, Grossman and Katz [3] have reported that injection of heparinized blood into the pulmonary artery of the dog decreased the air capacity of the lung. Withdrawal of blood resulted in a return of distensibility toward its original level, showing that the decrease in distensibility was due to the amount of intravascular blood rather than to intraalveolar transudate. In the open chest, compression of the pulmonary veins caused decreased distensibility, and release of pressure was followed by a return of distensibility. Compression of the aorta also decreased the air capacity of the lungs. Distensibility improved on compression of the main pulmonary artery, partial compression of both venae cavae and during the development of shock. The authors conclude that pulmonary distensibility varies inversely with the amount of blood in the pulmonary vessels.

Parin [4] has described a third moderator reflex, in addition to reflexes arising in the aortic arch and in the carotid sinus. He observed that increasing the pulmonary arterial pressure in experimental dogs always in-

* Presented at the Regional Meeting of the American College of Physicians in Montreal, September 23, 1949.
Received for publication April 17, 1950.

duced a fall in systemic blood pressure, which was accompanied by a diminution in pulse rate and an increase in systemic venous pressure.

Motley et al.[5] reported the effect of induced anoxia on pulmonary artery pressures in man. A mixture of 10 per cent oxygen in nitrogen was breathed by normal men, and studies of the pulmonary circulation were made by means of cardiac catheterization. Pulmonary hypertension was induced by this method, the pulmonary pressures returning rapidly to normal when the subjects were allowed to breathe air. During anoxia the cardiac output decreased slightly and the stroke volume decreased greatly, the latter largely because of increase in heart rate. Pulmonary vascular resistance increased only slightly.

Cournand[6] has shown by cardiac catheterization studies that the capacity of the *normal* vascular bed in the lungs is so great that the blood flow may be increased several fold with negligible pressure changes. Blood flow through the lungs is identical with that in the systemic circulation except for momentary differences and lower pressures in the right ventricle, pulmonary artery and pulmonary capillaries. Intrathoracic pressures affect the blood flow, pressures in the vessels and circulating blood volume in the lungs. Changes in the general level of pressure curves in the auricle, ventricle, pulmonary artery and veins are passive and are due to propagation of intrathoracic pressure. Variations in intrathoracic pressure influence venous return and the output of the right ventricle. He concludes that under physiologic conditions there is no clear evidence of vasomotor activity in the lungs.

The results of these experiments may be summarized as follows:

1. Pulmonary blood pressure and distensibility of the lungs depend upon the volume of blood actively circulating through the pulmonary vascular bed.

2. An abrupt increase in pulmonary arterial pressure induces a fall in systemic arterial pressure and a rise in venous pressure.

3. Acute anoxia in man produces pulmonary hypertension, which is accompanied by a decrease in cardiac output and stroke volume and a slight increase in pulmonary vascular resistance.

4. The volume of blood in the pulmonary vessels is governed by relative discharge of the two sides of the heart, and this is normally regulated by changes in the systemic circulation.

Hamilton's[7] discussion of the pulmonary disease manifestations of ankylosing spondylarthritis is a clear description of the manner by which persons with spinal arthritis acquire pulmonary fibrosis and the cor pulmonale. Immobility of the costovertebral articulations hinders respiration and renders cough ineffective. Upper respiratory infections, abdominal surgery or spinal anesthesia may lead to poor bronchial drainage, the development of bronchial plugs, with subsequent atelectasis, and pneumonitis from infection by organisms already present in the respiratory tract. His

pertinent remarks apply equally to other chest conditions in which there is interference with respiration and cough.

Evidence of coronary disease has been observed in persons who also showed strain upon the right ventricle resulting from one of several causes: kyphoscoliosis with marked chest deformity, spinal arthritis, thoracoplasty, pulmonary fibrosis, emphysema, and pulmonary vascular disease from mitral stenosis. Age at onset of circulatory symptoms was 47 or more. All the patients were found to have angina pectoris or congestive heart failure or both conditions. Electrocardiographic abnormalities were present in all but one case, but there was no typical electrocardiographic pattern of the combined disorders. Cardiac enlargement was the rule, but the enlargement was marked in only the three patients who had associated systemic hypertension. Sinus rhythm was present in all. A considerable degree of cardiac disability existed, but nearly half the patients were able to follow a gainful occupation with intervals of full disability.

Respiratory infections were disabling, as would be expected. Pneumonitis in the patients with angina pectoris led to severe prolonged chest pain of the usual type, which did not respond to nitroglycerin. One individual survived three attacks of myocardial infarction, each of which followed a pulmonary infection. Oxygen therapy was beneficial in every bout of respiratory infection for which it was given. Oxygen seemed particularly helpful in the anginal cases. Chemotherapy and antibiotics were used to combat respiratory infection.

The effect of digitalis was often disappointing. A low sodium intake and mercurial diuretics were more efficient methods of treatment for congestive failure. Patients with frequent anginal attacks and persisting pulmonary congestion were able to go several days with little or no nitroglycerin after an injection of mercurial diuretic. Theophylline preparations and antihistaminics were used with varying results. A régime of daily living and avoidance of exposure to respiratory infections insofar as possible, were considered basic treatment. Winter residence in a warm climate is recommended.

Two illustrative case reports follow.

Case Reports

Case 1. A physician was found in 1919 to have pulmonary tuberculosis with cavitation in the left upper lobe. He continued to show a positive sputum for 14 years, until a high left thoracoplasty was performed in 1933. After operation he gained weight and developed hypertension. In May, 1945, he suffered coronary thrombosis with infarction in the apical region of the heart. This illness left him with angina of effort. In the spring of 1947 an upper respiratory infection was complicated by pneumonitis; the anginal attacks became much worse, and electrocardiographic signs of fresh myocardial infarction were found.

In October, 1947, he was admitted to the hospital with cough and fever of two weeks' duration. A diagnosis of primary atypical pneumonia had been made. From the onset of this infection anginal seizures had been more frequent and prolonged, ap-

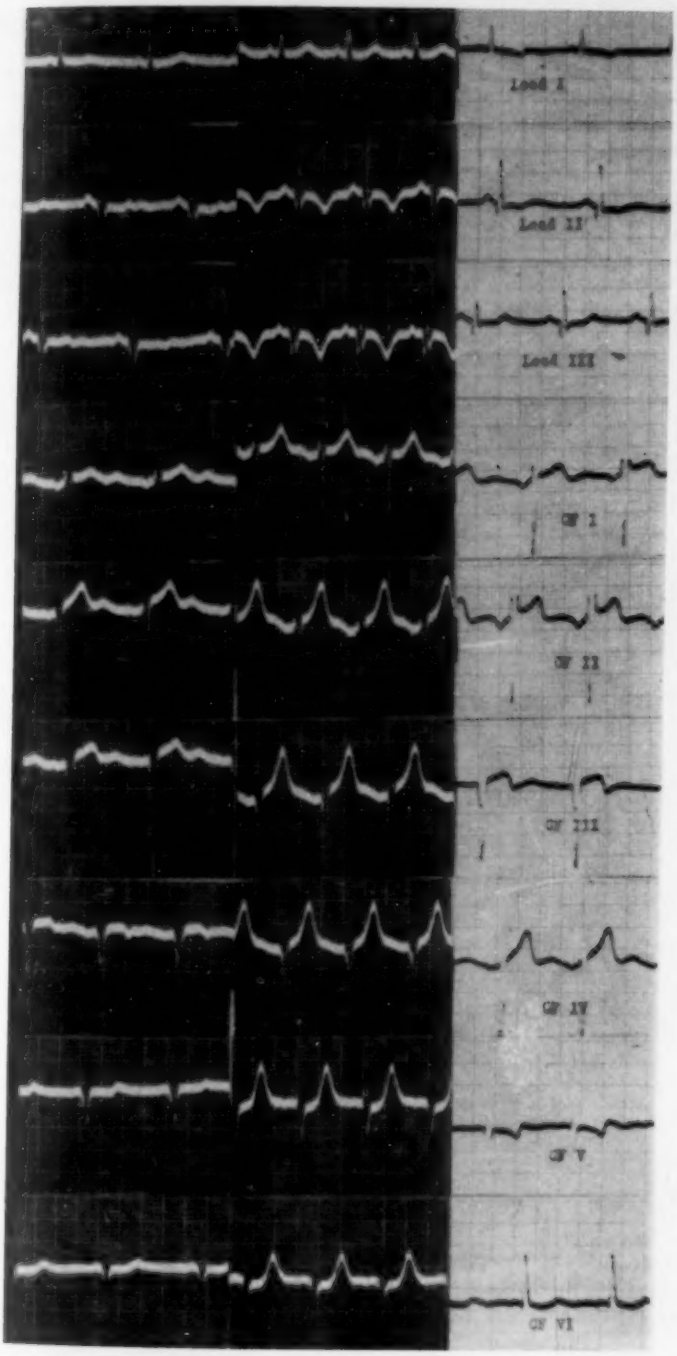

FIG. 1. *Case 1.* Electrocardiogram with the standard and six precordial leads. From left to right: (1) after effects of original anterior myocardial infarction; (2) new posterior infarction; (3) fresh area of anterior myocardial infarction.

pearing when he attempted to take food or without apparent cause. The attacks had not always responded to nitroglycerin, and opiate had been necessary.

He was afebrile. The blood pressure was 160 mm. Hg systolic, 90 mm. diastolic. The blood sedimentation rate was 41 mm. in one hour. The electrocardiogram showed residual effects of the two previous anterior infarctions. Oxygen and penicillin were ordered. In spite of oxygen therapy, daily opiate was required for relief of anginal pain. Three days after admission, a pericardial friction rub was present and a Q_3T_3 pattern had developed in the electrocardiogram (figure 1). Dicumarol was started. Anginal attacks subsided but reappeared when oxygen was not breathed. Six attempts were made to live outside the oxygen tent before it could be finally discontinued five weeks after admission. He was free from angina and able to be out of bed in the eleventh week after the beginning of the respiratory infection (figure 2).

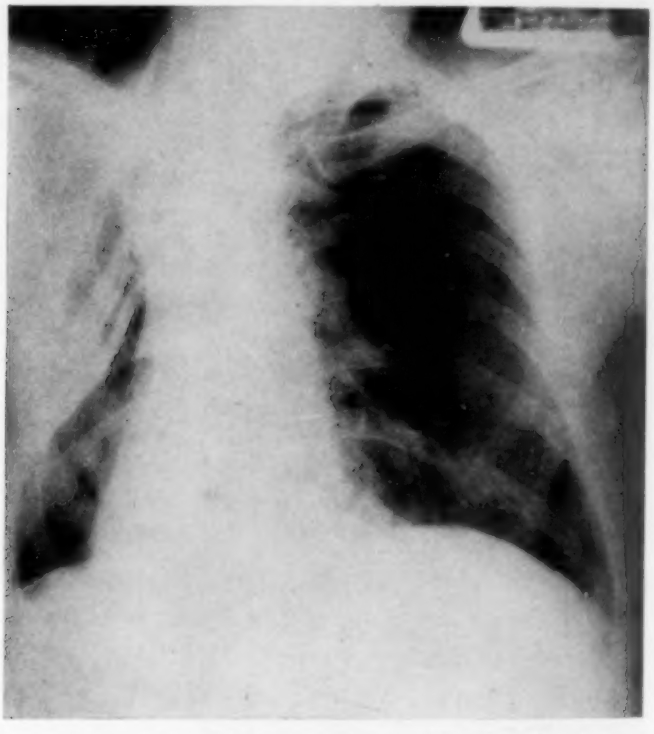

FIG. 2. *Case 1.* Effects of high left thoracoplasty with infiltration in the uncollapsed portion of the left lower lobe.

Another respiratory infection in February, 1948, confined him to bed with frequent anginal attacks. Immunizing doses of pneumococcus polysaccharide and influenza vaccine were employed. Cough and exacerbation of angina followed the influenza vaccine in October.

Penicillin sensitivity with transient arthritis was observed during treatment of tracheobronchitis in November, 1948. In January, 1949, he was hospitalized because of a chest infection accompanied by four or more daily attacks of angina. It was possible to use penicillin in conjunction with Pyribenzamine.

At present he is able to do office practice with only infrequent angina. He has mild hypertension with cardiac enlargement and a Grade 3 apical systolic murmur.

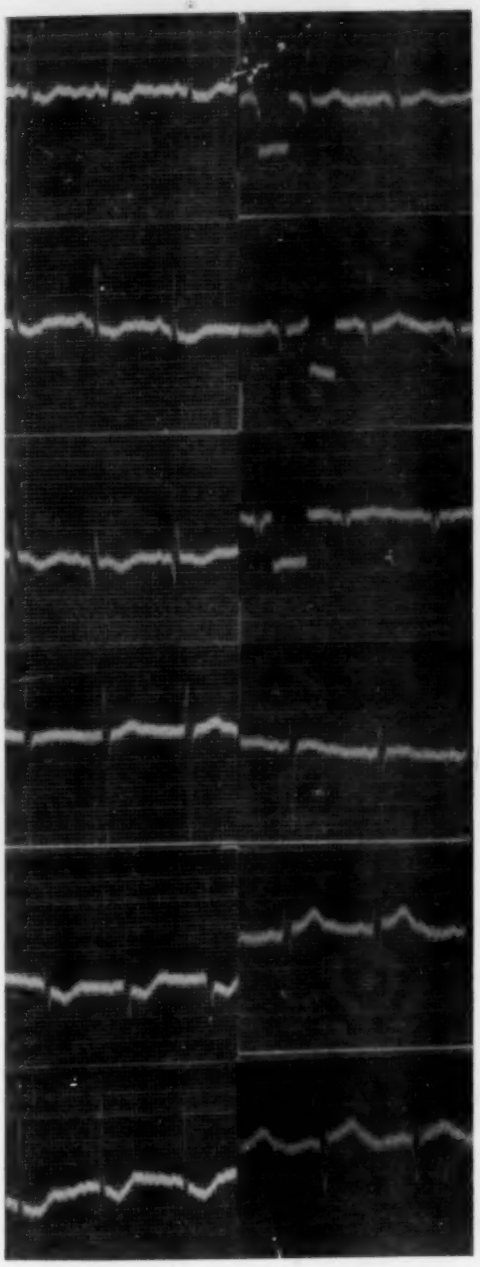

FIG. 3. *Case 2.* Electrocardiogram with standard and Leads CF_2, CF_4 and CF_5. Before the tracing at the left and that at the right after the severe attack of substernal pain accompanying pneumonia. Both tracings show Q waves in Leads II and III. Digitalis effect is marked in the first record.

His electrocardiogram is stable, showing intraventricular block with signs of old infarction.

If today's procedures in thoracic surgery had been available in 1933, this patient might have had a lobectomy or pneumonectomy instead of the thoracoplasty. It is interesting to speculate how much of his disability might have been prevented by extirpation in place of pulmonary collapse.

Case 2. A small, thin Danish woman of 66 years was seen in 1938 with a history of angina pectoris for two months. There had been a prolonged attack of substernal pain at the age of 63, from which she had made a good recovery. She had had severe scarlet fever in childhood and paroxysmal tachycardia since the age of 33.

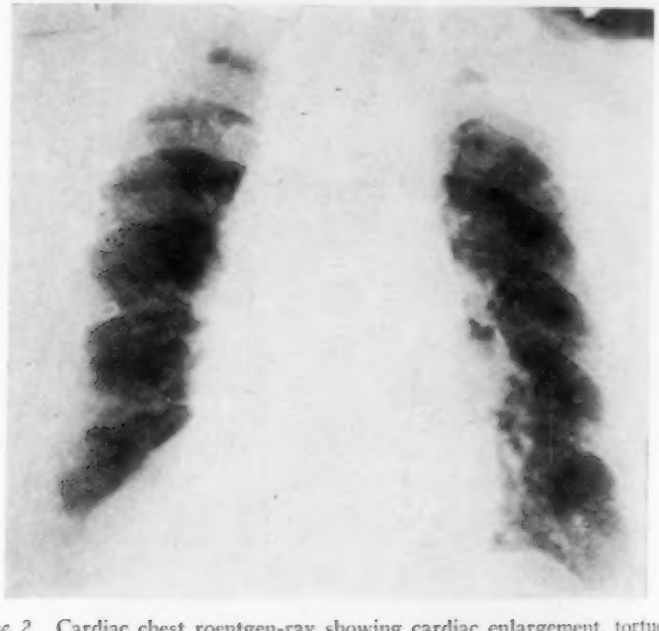

FIG. 4. *Case 2.* Cardiac chest roentgen-ray showing cardiac enlargement, tortuosity of the aorta and increased vascular markings, particularly in the lower lobes.

Examination revealed a blood pressure of 186 mm. Hg systolic and 110 mm. diastolic. There were cardiac enlargement, an accentuated aortic second sound and a mitral diastolic murmur. The radical and brachial arteries were thickened. Chest expansion was diminished, and fine moist râles were heard over the lower lobe of the right lung.

During 1938 the blood pressure gradually fell to normal. The auricular paroxysmal tachycardia has been well controlled by quinidine. Angina has continued to be frequent during the 11 year period of observation. Breathlessness on exertion has increased and nocturnal dyspnea has occurred at intervals. There was a recurrence of hypertension from 1942 to 1945. Theophylline preparations, which had been given for eight years, were supplemented by digitalis and a low sodium diet in 1946. At times she has eaten poorly and has shown glossitis. In March, 1949, severe and prolonged anginal pain required opiate. Signs of pneumonia were found and the infection responded to penicillin, with temporary relief of angina.

Following recovery from the pneumonia, the patient had six to 10 attacks of angina a day and breathlessness was increased. A mercurial diuretic program, with injections at regular intervals, was instituted. The dyspnea improved on this régime, and it has been found that anginal attacks disappeared for two or three days after diuresis, then returned with daily increase in frequency. At no time have subcutaneous edema or venous engorgement been seen.

Roentgenogram of the chest shows cardiac enlargement, tortuosity of the aorta and increased vascular markings (figure 3). The abnormalities in her electrocardiogram may be explained as digitalis effect (figure 4).

This case shows a prolonged course of mitral stenosis and arteriosclerotic heart disease with paroxysmal tachycardia, severe angina pectoris and congestive heart failure. It is believed that the pulmonary vascular disease resulting from mitral stenosis has added a considerable burden to the heart's load and has been a factor in the intractable angina. The appearance of severe and prolonged anginal pain during pneumonia resembles the response to pulmonary infection in case 1. Relief of pulmonary hypertension by means of induced diuresis has caused temporary cessation of anginal seizures. Anginal attacks begin again when pulmonary congestion has reappeared.

Summary

A description is given of the symptoms, findings and course in a group of persons showing coronary sclerosis and pulmonary hypertension. It is seen that factors increasing the blood pressure in the pulmonary circuit lead to congestive heart failure or a marked increase in angina pectoris, even to the onset of cardiac infarction. Medical management of patients with the two disorders is discussed.

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LIVER FUNCTION STUDIES DURING CORTISONE THERAPY *

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The study dealt with herein was undertaken to determine if any of the usual clinical liver function tests change in any way under cortisone therapy. It is well known that the adrenal cortex is concerned with protein,[1, 2] glucose [3] and fat [4, 5] metabolism. It has even been reported that the administration of ACTH will produce a fatty liver in the experimental animal, although this can be prevented by the administration of glucose.[4] Furthermore, patients with Cushing's syndrome frequently have hypercholesteremia, and patients with adrenal insufficiency tend to a low serum cholesterol.[7] A marked hypercholesteremia was observed in rabbits after adrenal homotransplantation or injection of adrenal cortical extracts.[8] It seemed appropriate, therefore, to study liver function in humans under treatment with cortisone.

Method of Study and Results

Complete studies were done on 25 cases. Table 1 is an example of the protocol employed, the case being that of amyotrophic lateral sclerosis. The following determinations were included: thymol turbidity, serum bilirubin, van den Bergh, icterus index, prothrombin time, total serum cholesterol, cholesterol-ester ratio, total serum proteins and AG ratio, bromsulfalein test and serum esterase. All tests were obtained during the control period, at least once or more during therapy, and then repeated at the time therapy was discontinued. Twenty-three of these cases had no known liver disease, while two had chronic hepatitis.

The type of case treated and the general plan of therapy are shown in table 2. Initial dosage schedules varied from 100 mg. daily in the first cases treated to a maximum of 300 mg. daily in later instances. Total dosages varied from 1.65 gm. to 10.3 gm. The diet used during these cortisone studies was the regular hospital diet, containing approximately 100 gm. protein, 135 gm. fat, 330 gm. carbohydrate and 3,000 calories.

Our results indicate that cortisone therapy, even for periods up to three months and in amounts up to 10 gm., produced no startling change in any

* Received for publication December 18, 1950.

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Sponsored by the Veterans Administration and published with approval of the Chief Medical Director. The statements and conclusions published by the authors are the result of their own studies and do not necessarily reflect the opinion or policy of the Veterans Administration.

This work is part of a coördinated program for the study of Cortisone conducted by the Research Division of the Veterans Administration.

TABLE I

LRE. Diagnosis: Amyotrophic Lateral Sclerosis
Age: 50
Days of Treatment: 31
Total Dose: 2,975 mg.

Tests	Before	During	After*
Thymol turbidity	5 mu.	10.5 mu.	5 mu.
Total cholesterol	220 mg. %	167 mg. %	161 mg. %
Cholesterol-ester ratio	53%	57%	61%
Total serum protein	6.2 gm. %	5.9 gm. %	6.0 gm. %
Serum globulin	3.9 gm. %	2.1 gm. %	1.9 gm. %
Serum bilirubin	Below 0.5	Below 0.5	Below 0.5
BSP	0% in 30 min.	0% in 30 min.	0% in 30 min.
Serum esterase	17.8 micromoles phenol/ml.	17.8 micromoles phenol/ml.	14.7 micromoles phenol/ml.
Thorn test	No. 1 306 Eos./cu.mm.	No. 1 20 Eos./cu.mm.	No. 1 213 Eos./cu.mm.
	No. 2 236 Eos./cu.mm.	No. 2 9 Eos./cu.mm.	No. 2 180 Eos./cu.mm.

* These tests were all done within one to three days of completion of cortisone therapy.

of these liver function tests. This was true even in cases of known liver disease.

The only tests which showed any interesting changes were the thymol turbidity, total serum cholesterol, cholesterol-ester ratio and the serum esterase. We have listed the control values, the maximal and minimal

TABLE II

Shows the type of cases treated in this study, the total dosage and the duration of therapy. The case numbers used in subsequent tables correspond to the numbers in this table.

	Age	Diagnosis	Days Treated	Total Dose mg.
1 JHB	55	Rheumatoid arthritis	28	3,475
2 MB	30	Dermatomyositis	38	6,600
3 RJB	61	Rheumatoid arthritis	25	4,450
4 RRC	69	Rheumatoid arthritis	28	1,650
5 WMD	61	Rheumatoid arthritis	30	3,100
6 LRE	50	Amyotrophic lateral sclerosis	31	2,975
7 AF	32	Rheumatoid arthritis	14	2,800
8 RLH	35	Rheumatoid arthritis	27	3,325
9 CGJ	32	Hodgkin's disease	30	6,000
10 JPK	56	Possible periarteritis nodosa	29	3,600
11 RCL	37	Dermatomyositis	92	10,300
12 EAM	37	Multiple sclerosis	14	2,125
13 CAM	56	Rheumatoid arthritis	96	5,900
14 RN	56	Rheumatoid arthritis	26	5,200
15 CJP	55	Rheumatoid arthritis	31	5,600
16 JLP	23	Rheumatoid arthritis	15	2,500
17 DWS	54	Rheumatoid arthritis	39	2,900
18 JCS	36	Rheumatoid arthritis	20	3,600
19 WRT	64	Rheumatoid arthritis	83	9,600
20 GVC	64	Rheumatoid arthritis	52	6,450
21 JAW	37	Rheumatoid arthritis	31	4,000
22 SM	23	Regional ileitis	16	2,800
23 FLS	35	Rheumatoid arthritis	23	4,300
24 AK	26	Chronic hepatitis	14	2,100
25 CRW	32	Chronic hepatitis	18	2,300

values observed during therapy and, in some instances, the values obtained after therapy was discontinued. The values for the thymol turbidity tests shown in table 3 have been artificially grouped so that those showing an elevation are listed first, those with no change next, and those showing a drop last. The upper limit of normal for the thymol turbidity determination employed at this hospital is 10.5 MacLagan Units. It will be noted that seven cases (MB, CVC, CJP, RCL, JPK, AF, CAM) showed a definite increase during cortisone administration, while six cases had a slight increase. On the other hand, in three instances (WMD, DWS, WRT), the

TABLE III

Changes in Thymol Turbidity during Cortisone Therapy

Patient	Before	During		After*
		Maximum	Minimum	
2	10.5	22	10.5	
20	10.5	22	16.0	
15	10.5	22	5.0	
11	5.0	16	5.0	16.0
10	16	22		22
7	22	34		
13		22	16.0	16
6	5.0	10.5		5.0
18	5.0	10.5		10.5
1	5.0	10.5	5.0	10.5
14	5.0	10.5		
16	2.5	5.0		
3	10.5	10.5	5.0	10.5
4	10.5	10.5	5.0	10.5
8	2.5	5.0		5.0
9	5.0	5.0		5.0
12	5.0	5.0		5.0
22	5.0	5.0		5.0
21	10.5	5.0		5.0
5	34.0	10.5		16.0
17	34.0	28.0		
19	34.0	34.0	22.0	40.00

* These tests were all done within one to three days of completion of therapy.

elevation of the thymol turbidity which was observed prior to therapy tended to decrease in association with cortisone administration. When these alterations in the thymol turbidity test were first observed, it seemed advisable to employ an additional test, the cephalin flocculation determination. Repeated cephalin flocculation tests were done in six cases, and no definite trend was noted.

The changes in the total serum cholesterol which were observed are shown in table 4. These have been grouped in the same manner as the thymol turbidity. Increases of more than 40 mg. per cent were noted in the first eight individuals listed. The average of the control cholesterol was

170 mg. per cent; the average of the maximal values observed during therapy was 187 mg. per cent, a difference of approximately 10 per cent.

Selected examples of the changes in the cholesterol-ester ratio are shown in table 5. While two cases exhibited an increase of greater than 20 per cent during cortisone, this was contrasted by a decrease of more than 20 per cent in two other cases. The average for the control values was 56.3 per cent, of the maximal values during therapy 60.2 per cent, of the minimal values 48.5 per cent.

The serum esterase values showed a slight decrease in 20 of 21 cases studied (table 6). This change was consistent though never marked. For

TABLE IV

Changes in Total Serum Cholesterol during Cortisone Therapy

Patient	Before	During	
		Maximum	Minimum
5	115	266	
21	150	233	194
10	146	228	159
20	202	275	141
17	151	221	
15	171	220	158
9	180	221	195
8	151	189	138
2	166	207	118
1	120	158	118
3	171	205	119
19	154	179	169
7	156	177	
13	141	162	158
14	175	176	131
11	192	207	149
23	246	256	
16	123	129	75
8	167	168	168
18	209	209	197
12	220	194	
14	189	158	
6	220	167	162
Average	170	187	152

example, the average of the control values was 16.2, of the maximal values observed during therapy 14.4, of the minimal values 13.7. In only three instances did the serum esterase during therapy drop below a level of 10 micromoles of phenol/ml., which is considered to be the lower level of normal.[8]

Two cases of chronic hepatitis were followed closely while on cortisone therapy. The first was that of a 26 year old nurse who was admitted to the hospital with a diagnosis of acute hepatitis. The icterus index was 27, serum bilirubin 6.8 mg. per cent, van den Bergh diphasic, thymol turbidity 34 MacLagan units. She received a seven day course of aureomycin with-

TABLE V

Changes in Cholesterol-Ester Ratio during Cortisone Therapy

Patient	Before	During		After*
		Maximum	Minimum	
19	44	73	43	46
20	57	78	45	
23	54	72		
17	51	63		
3	57	69	41	
4	48	57	42	
2	46	60	40	
11	54	62	50	40
13	63	49		51
15	70	59	50	
22	75	49		
1	78	47	46	64

* These tests were all done within one to three days of completion of cortisone therapy.

out apparent benefit. At the time cortisone was started, three months later, she still had exhibited no improvement in the tests of liver function or in the degree of icterus, and the possibility of cirrhosis as an end stage in the process seemed likely. The first course employed 100 mg. of cortisone daily over a seven day period and, after a lapse of three weeks, an additional week of 200 mg. daily was given. The tests of liver function were in no way altered; the icterus index was 26 before treatment and 22 afterward, and the thymol turbidity remained at 22 MacLagan units. During therapy a transient improvement in sense of well being was observed, and the appetite was considerably stimulated. This patient was finally discharged from the hospital six months after admission and at that time still had

TABLE VI

Changes in Serum Esterase during Cortisone Therapy

Patient	Before	During		After*
		Maximum	Minimum	
2	10.6	7.8		
19		10.6	7.4	10.3
3	15.7	13.9	13.9	
4	20.8	19.3	17.8	13.9
5	14.9	10.3		12.3
6	17.8	17.8	14.7	
7	15.9	12.7	10.6	
8	17.2	13.3		15.9
15	15.7	13.9	12.3	
16	17.8	16.8	13.9	
18	25.6	23.5	21.6	21
1	15.7	13.1		11.4
22	9.2	12.3		13.5

* These tests were all done within one to three days of completion of cortisone therapy.

jaundice, an icterus index of 22, thymol turbidity of 10.5 MacLagan units, and fetor hepaticus.

The other case, a 32 year old male, had been treated for six months with a diagnosis of infectious hepatitis, and at the end of that time still had clinical icterus, a thymol turbidity of 34 MacLagan units, and a reversal of the albumin-globulin ratio. Liver biopsy at that time revealed portal cirrhosis, grade II, with cellular infiltrate compatible with subacute inflammation. During an 18 day course of cortisone, in which he received 2,300 mg., his appetite and sense of well-being improved moderately. There was no significant change in the liver function studies, however, and a second liver biopsy after therapy closely resembled the first. Here again, the course of chronic hepatitis was not altered significantly with cortisone therapy.

Our experience with these two cases would seem to indicate that cortisone has little value in the treatment of chronic hepatitis, aside from its "tonic" effect. This ability of the drug to augment appetite, however, may be of considerable aid in the management of the anorexia which sometimes presents a serious problem in liver disease. On the other hand, these two cases make one feel rather certain that cortisone has no deleterious effect on liver function as measured by the usual clinical tests.

Discussion

The results of this investigation indicate that cortisone does not produce any significant changes in liver function with the tests used in this study. Minimal changes were noted in the thymol turbidity, serum cholesterol, cholesterol-ester ratio, and serum esterase. Changes in thymol turbidity might be explained by alterations in the electrophoretic pattern. Such studies have not been done at this hospital.

With special reference to the serum cholesterol, Adlersberg and coworkers [9] have recently studied the serum lipid changes in 15 persons receiving cortisone therapy. They found an average increase of 15 per cent in the total serum cholesterol. This can be compared with our average maximal increase of 10 per cent.

Summary

Complete studies of liver function during cortisone therapy in 25 patients indicated that cortisone produced no significant change in these tests. The slight changes noted in the thymol turbidity, total serum cholesterol, cholesterol-ester ratio and serum esterase are discussed. Further, we have no evidence that cortisone, when given in two cases of liver disease, impaired hepatic function in any way.

Acknowledgment

The authors wish to acknowledge the assistance and coöperation of Dr. Thad. P. Sears, Dr. Martin G. Goldner, and Dr. G. C. Krebs during the initial phases of this study.

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THE CLINICAL APPLICATION OF PITUITARY ADRENOCORTICOTROPIC AND ADRENAL STEROID HORMONES *

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BACKGROUND AND FUNDAMENTAL CONCEPTS

THE history of the pituitary-adrenal system, at least from the standpoint of the clinical physiologist, may be divided arbitrarily into three periods. The *first* began with the masterly description by Thomas Addison [1] in 1855 of the disease which has since borne his name, and with the demonstration a year later by Brown-Séquard [2] that extirpation of the adrenals in laboratory animals resulted in the death of the animals. The *second*, or period of intensive experimentation, had its inception with the demonstration in 1927, by Hartman, MacArthur and Hartman,[3] and by Rogoff and Stewart,[4] independently, that adrenal cortical extracts would prolong the survival period of adrenalectomized animals. The *third* or clinical period was initiated with the demonstration by Hench, Kendall, Slocumb and Polley [5] of the effects of Compound E and of pituitary adrenocorticotropic hormone in patients with rheumatoid arthritis.

During the second period, the contributions to the knowledge and understanding of pituitary and adrenal physiology were so numerous as to make it prohibitive to list even the more important contributions in the bibliography of a predominantly clinical paper. Among those investigators and clinicians who contributed very greatly to the field during this period, however, may be mentioned, in alphabetical sequence: Albright, Browne, Butler, Collip, the Coris, Cushing, Evans, de Fremery, Houssay, Ingle, Kendall, Loeb, Long, Mason, Pfiffner, Reichstein, Selye, Smith, Swingle, Talbot, Thorn, Zwemer, and many others, including the collaborators of the above.

As the result of the contributions of these men, the following concepts have been generally accepted for a period of 10 or more years:

* Morning Lecture, presented at the Thirty-second Annual Session of the American College of Physicians, St. Louis, Mo., April 11, 1951.

From the Institute for Metabolic Research, Highland Alameda County Hospital, Oakland, California.

Any original work here reported represents the combined work of the author and his co-workers, including Lenore Boling, M.D., Sheldon Margen, M.D., George D. Michaels, Ph.D., and John W. Partridge, M.D., aided by the following technical assistants: Carl T. Anderson, Nancy C. Dawson, E. Rosalie Greer, Eleanor E. Kipp, Judith M. Lange, Gerald Liebert, Nancy J. McKillican, Florence Olson and Sadie Smyrl.

Grateful acknowledgment is made to Dr. Edward Henderson, Medical Director of Schering Corporation, for supplies of testosterone propionate; to Dr. John Mote, Assistant General Manager of the Armour Laboratories, for supplies of ACTH; to Dr. Augustus Gibson, Executive Director of the Medical Division of Merck & Company, for supplies of cortisone; and to Dr. Warren Cox, Director of Research of the Mead Johnson Research Laboratories, for supplies of Lonalac which have been used in some of the studies here reported.

1. That the adrenal cortex is essential to life.

2. That the adrenal cortex is vitally dependent upon the anterior pituitary for its normal functional activity.

3. That in a physiologic sense, at least three types of adrenal cortical hormones exist. One of these regulates *salt and water metabolism* through its effect upon the kidney. The second is *protein anabolic* (i.e. growth

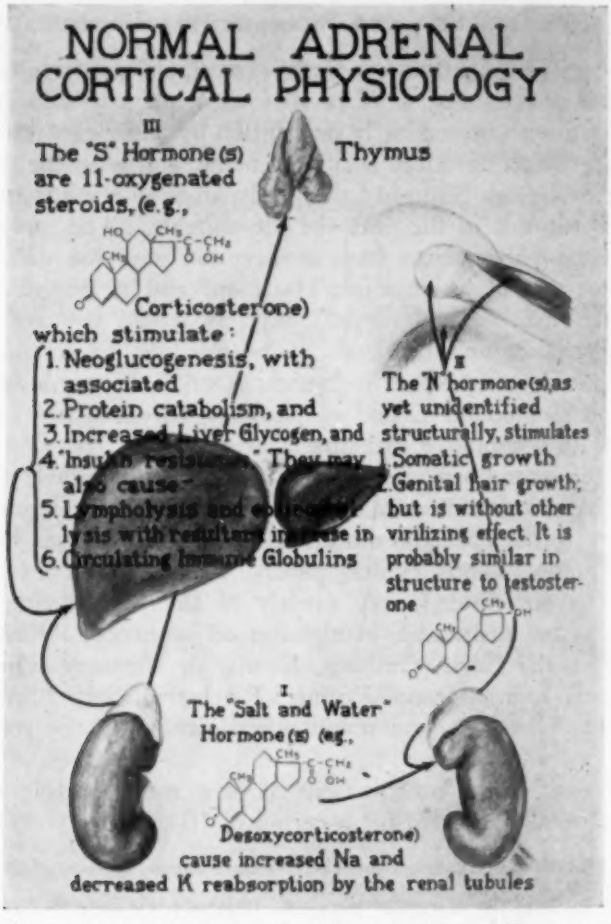

FIG. 1. Fundamental concepts of adrenal cortical physiology. These are undergoing constant modifications and additions.

promoting), mildly androgenic, and responsible for the growth of axillary and pubic hair in the female. (This hormone does not put in its appearance until the time of puberty.) The third *stimulates protein catabolism*, causes significant neoglucogenesis, and is associated in some way with specific or nonspecific resistance to disease. These properties of adrenal cortical steroids are shown diagrammatically in figure 1.

Largely as the result of the work of Albright and his collaborators,[6] it is generally accepted that excessive production of the third type of hormone results in Cushing's syndrome (figure 2), and that excessive production of the second type produces the adrenal genital syndrome (figure 3).

There is little in the above observations to suggest that adrenal-cortical stimulating hormone, or any adrenal hormone per se, would be of value to a

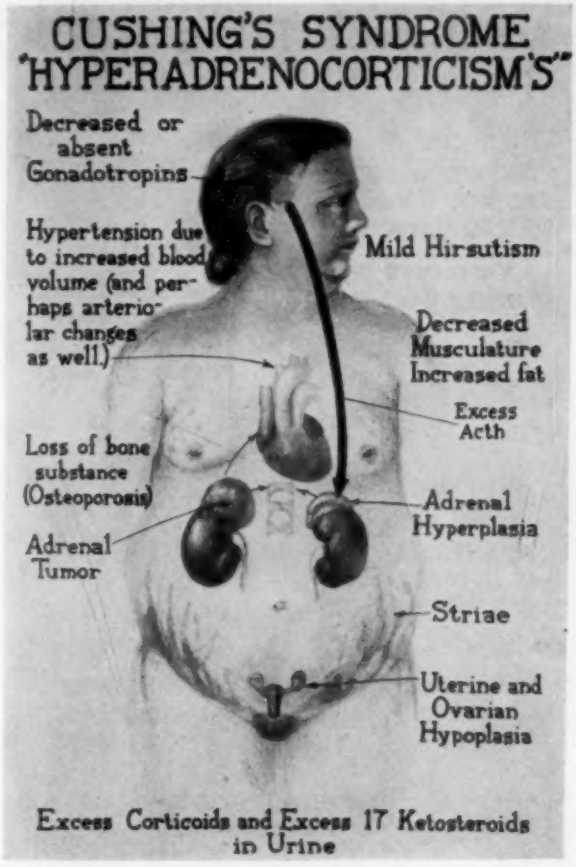

FIG. 2. Prolonged, excessive ACTH or cortisone administration can produce essentially all the changes which are found in spontaneously occurring Cushing's syndrome.

patient with rheumatoid arthritis, bronchial asthma, or any of the large number of other disease states which have been shown to respond to the administration of ACTH or cortisone.

As late as February, 1949 (just three months before the report by Hench et al.), a group of investigators was informally discussing the strange finding that so-called pituitary "growth hormone" failed to make any humans grow or retain nitrogen. Dr. Hugh Long, of Yale, one of the pioneers in

the pituitary-adrenal field, commented that the only really potent pituitary hormone available in relatively pure form for human use was ACTH, and that this appeared to have little in the way of potential clinical usefulness, particularly in view of its diabetogenic tendencies.

Two months later, when the Mayo group reported their initial observations on the effects of cortisone and ACTH in patients with rheumatoid

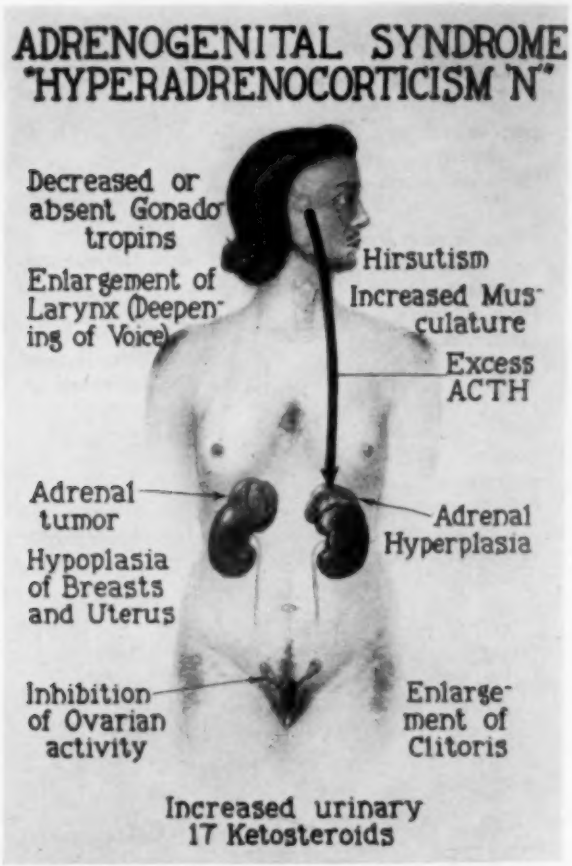

FIG. 3. Hirsutism, with variable degrees of virilization, may result from adrenal hyperactivity. The precise chemical identification of this type of adrenal hormone has not yet been accomplished.

arthritis, I believe that most investigators who had worked with pituitary and adrenal preparations heard the report with some skepticism. The skepticism, however, did not persist. It was found that the same results obtained in Rochester were obtained with equal regularity and to the same degree with ACTH and with cortisone by investigators elsewhere. Even more startling, in the space of a few weeks and months it was found that

the administration of these substances to patients with many diseases resulted in rapid and impressive improvement in their disease states. So wide a variety of apparently unrelated diseases, both in terms of etiology and manifestations, was benefited that for a time there appeared to be a lack of any common denominator to explain the effects obtained.

In October, 1950, however, Dr. Maxwell Finland and his co-workers, at the instigation of Dr. John Mote,[7a-b] reported an observation which to my mind began to bring a bit of order out of chaos. They found that the administration of ACTH, without any other kind of therapy, to a patient with a severe pneumococcus pneumonia resulted in prompt and complete disappearance of all symptoms and in most of the signs of the clinical pneumonia. Despite this clinical change, however, the blood culture which had been positive prior to the administration of ACTH remained positive for a period

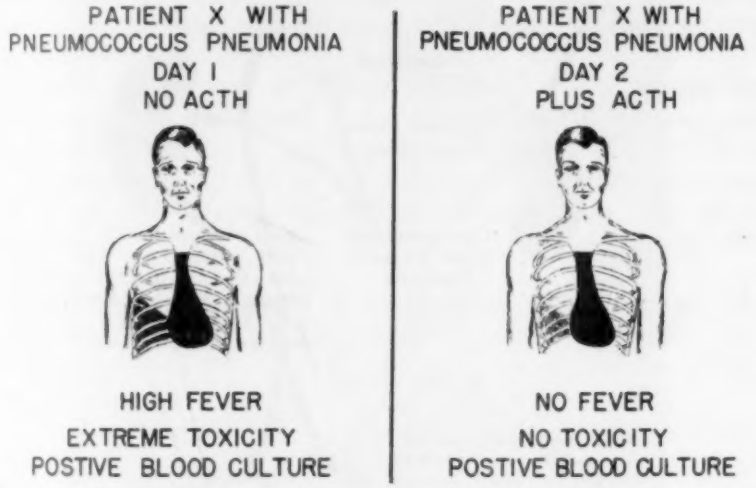

FIG. 4. Effects of ACTH in specific infectious processes. It is apparent that the clinical improvement is *not* related to bacteriostasis.

of two more days, and then became negative (figure 4). Antipneumococcal antibodies and cold agglutinins appeared at the anticipated time. From this observation two things seemed apparent: *first,* that the adrenal steroids resulting from ACTH administration *exerted no effect upon the growth of the organisms which produced the disease;* and, *second,* that the adrenal steroids resulting from ACTH administration *did, however, completely neutralize the effect of the toxins produced by the organisms upon the cells of the host,* and hence eliminated the clinical symptoms of pneumonia.

A pharmacologic agent to produce such an "antitoxic" effect might act in one or more of three ways:

First, it could destroy the toxin or adsorb it, in the same sense that diphtheria antitoxin administered to a patient with diphtheria neutralizes the

diphtheria toxin. Such a concept could very well fit in with the effects of adrenal cortical hormones upon leukocytes reported by Dougherty and White.[8a-b] These investigators believe that the adrenal-steroid-induced breakdown of lymphocytes and other cellular elements results in increase in the titer of certain of the circulating globulins.

Second, an antitoxic effect could be exerted at the level of the cell membrane. One might very well conceive of adrenal steroids so affecting per-

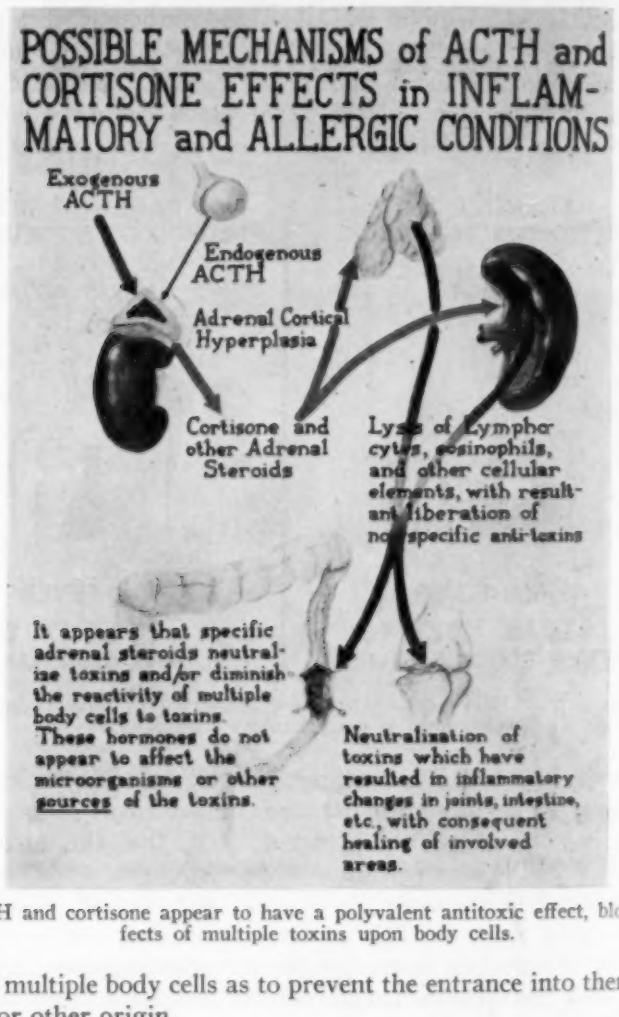

FIG. 5. ACTH and cortisone appear to have a polyvalent antitoxic effect, blocking the effects of multiple toxins upon body cells.

meability of multiple body cells as to prevent the entrance into them of toxins of bacterial or other origin.

The *third* possibility would be that the adrenal steroid acts within the cell itself, in some way protecting enzyme systems and preventing the toxin from disrupting the intracellular machinery.

We have one observation which, while inconclusive, suggests that at

least a portion of the effect may be within the cell itself. A patient with tetanus of severe degree was treated with ACTH. He had previously received huge amounts of tetanus antitoxin without effect. At the time ACTH was begun, he was in opisthotonos and was having recurrent convulsive seizures. Within six hours he was able to sit up and to swallow. Within 48 hours, however, his condition had regressed to some degree, probably because of inability on the part of his adrenals to continue to respond to ACTH, for unknown reasons. While we were considering the advisability of co-administering cortisone, the patient had a fatal spasm of the glottis and died before tracheotomy could be performed. His adrenals at autopsy examination were found to be small, substantiating the concept of the inability of these organs to continue to respond to adrenocorticotropic hormone. Since it is assumed that patients with advanced tetanus are unable to respond to tetanus antitoxin because of the fixation of toxin *within the cell*, it seems probable that the initial effect of the hormone was exerted directly within the cell.

The dramatic effects of ACTH and cortisone in the management of patients with allergic states, such as the dermatoses, hay fever and asthma, initially reported by Bordley, Harvey, Howard and Newman,[9] Randolph and Rollins [10] and Rose,[11] and subsequently by many clinicians and investigators,[12a-g] can be adequately explained on the basis of the foregoing if one assumes that the adrenal steroids block the effect of circulating allergens upon the tissue cells.

The observation that patients who had previously had strongly positive tuberculin skin reactions became tuberculin negative [13] while receiving ACTH or cortisone would also fit in very well with this concept of blockade between toxin and peripheral cell.

If one applies this same line of reasoning to the so-called collagen diseases and to other diseases of unknown etiology in which ACTH and cortisone are capable of producing great clinical improvement, he could postulate that rheumatoid arthritis, for example, is a disease attributable to a circulating toxin of unknown origin with an impressive ability to damage joint tissues, and that the effect of the hormones is merely to interpose a block between the toxin and the cells of the joint (figure 5). The latter, while so protected, undergo rapid repair and reversion toward normal.

It appears probable, then, that the observation of ACTH effect in patients with pneumococcus pneumonia, a disease of known etiology, has enabled us to have some understanding of the effects of ACTH and cortisone in the multiple diseases of unknown etiology in which the hormones appear to have great clinical usefulness.

Clinical Application

In considering the clinical application of any pharmacologic agent, it is desirable that one have an adequate knowledge of the tissue pathology, the

bacteriology and the pathologic physiology of the disease state to be treated, and an equally well defined knowledge of the pharmacodynamic properties of the drug in question. Thus, one decides to administer a mercurial diuretic to a patient suffering from congestive heart failure on the basis of simple and concise reasoning. The same statement may be made in regard to the decision to give penicillin to a patient known to have pneumonia caused by the pneumococcus.

In the case of ACTH and cortisone, the indications are by no means so clear cut, since many of their pharmacodynamics are still obscure, and many of the diseases which respond to their administration are of unknown etiology. The further well-proved ability of these agents to cause undesirable effects in some individuals—in terms of edema, hypertension, hyperglycemia, glycosuria and even permanent diabetes, disordered mental states, muscle cramps and weakness, possibly as the result of breakdown of protein tissue in general and of potassium loss in particular—indicates a very great need for the specification of definite criteria for the administration of these agents.

One may list such criteria in the form of questions:

1. Is the diagnosis well established? If not, will additional diagnostic procedures further clarify the picture?

2. Will any other therapy adequately control the disease? If the answer is in the affirmative, at the present time such therapy should be used without question. It goes without saying that the use of a specific chemotherapeutic agent in an infectious disease of average severity represents much more rational therapy than the use of a nonspecific "blocking agent."

3. If other adequate therapeutic agents are not available, what are the relative hazards involved in the administration of ACTH and/or cortisone? For example, the presence of hypertension or of a damaged myocardium would make one consider the administration of ACTH or cortisone with some concern. The final decision obviously rests upon a careful weighing of the pros and cons by the physician responsible.

4. Is one justified in believing that a short course of hormone therapy will result in a permanent or a semipermanent remission of the disease process?

5. If not, is it probable that long continued administration will produce progressive improvement?

6. If the previous answer is in the affirmative, is the patient able to pay for the hormones over a prolonged period of time? One sees no unhappier individual than the patient with rheumatoid arthritis who has shown impressive response to therapy and who then relapses because of inability to purchase further medication. The addition of a flat pocketbook to his original disease represents no medical triumph.

In attempting to answer some of the above questions, it may be well to summarize a portion of the accumulated experience of the past two years

dealing with long-term and short-term observations in patients who have been treated with ACTH and cortisone. To do this, one may arbitrarily divide disease states into certain specific categories in terms of their relative responsiveness to the hormones (table 1).

TABLE I

1. *Conditions in Which ACTH-Cortisone Represent True Substitution Therapy.*
   a. Panhypopituitarism.
   b. Addison's disease.
2. *Conditions in Which ACTH-Cortisone Administration May Be Mandatory.*
   a. Generalized peritonitis.
   b. Severe systemic infections which do not respond adequately to chemotherapy.
   c. Inflammatory conditions of the eye.
   d. Burns and severe shock generally.
   All of the above in conjunction with indicated chemotherapy!
3. *Conditions in Which ACTH-Cortisone Are of Considerable Value.*
   a. Adrenogenital syndrome. (Cortisone is indicated; ACTH is contraindicated.)
   b. Allergic (hypersensitivity) syndromes.
   c. Colitis (ulcerative).
   d. Dermatomyositis.
   e. Gout.
   f. Hypoglycemia (idiopathic).
   g. Pemphigus.
   h. Reiter's syndrome.
   i. Rheumatoid arthritis.
   j. Scleroderma.
4. *Conditions in Which the Effects of ACTH-Cortisone Are Highly Variable.*
   a. Anorexia nervosa.
   b. Eclampsia.
   c. Hematologic disorders.
   d. Hodgkin's disease.
   e. "Hypoadrenocorticism, functional."
   f. Liver damage, acute and chronic.
   g. Lupus erythematosus.
   h. Periarteritis.
   i. Psoriasis.
   j. Renal disease.
   k. Rheumatic fever.
5. *Diseases in Which ACTH-Cortisone Should Be Used Only Under Controlled Investigative Conditions.*
   a. Hypertension.
   b. Neoplasms.
   c. Neurologic diseases (non-bacterial).
   d. Psychoses.
   e. Syphilis.
   f. Thyroid disease.
   g. Tuberculosis.
   h. Multiple diseases and syndromes which still remain to be critically evaluated.
6. *Conditions in Which ACTH-Cortisone Are Relatively or Absolutely Contraindicated.*
   a. Adrenogenital syndrome. (ACTH contraindicated; cortisone indicated.)
   b. Cushing's syndrome.
   c. Cardiac failure.
   d. Diabetes.
   e. Osteoporosis.
   f. Peptic ulcer.

DISEASES IN WHICH ACTH OR CORTISONE REPRESENT TRUE SUBSTITUTION THERAPY

"Panhypopituitarism": ACTH administered to the patient with complete or nearly complete ablation of the pituitary will greatly improve his clinical

status. It is obvious that he will require other hormonal therapy as well, particularly desiccated thyroid and gonadal steroid hormones (since dependable thyrotropin and gonadotropin are not available). The maintenance dose of ACTH in such patients is probably less, perhaps considerably less, than 10 mg. daily (in terms of the Armour LA–1–A standard).[14, 15]

Maintenance dosage of cortisone appears to vary from 10 to 50 mg. Concomitant desoxycorticosterone will also be required by some of the patients who receive cortisone without ACTH.

Addison's Disease (Hypoadrenocorticism): For obvious reasons, ACTH is without effect in the patient with no adrenals. In the patient with suspected but still unproved adrenal cortical insufficiency, the demonstration of the ability or lack of ability to respond to ACTH in terms of a fall in eosinophils, as described by Thorn and his collaborators,[16] is of great value.

In the patient with true Addison's disease, the administration of cortisone results in great clinical improvement. Maintenance dosage may be as little as 10 mg. daily.[17a-b] Co-administration of desoxycorticosterone, for its much greater sodium retaining effect, is essential in some of these patients.[18]

Conditions in Which ACTH-Cortisone Administration May Be Mandatory

Under this heading will be included arbitrarily those diseases in which a prompt response is obtained, and in which therapy may be discontinued in a short period of time. In this connection, it is well to emphasize that *ACTH and cortisone cure nothing.* As previously indicated, however, *they do interpose a block between a host of toxins and a multitude of peripheral cells,* thus giving the body cells an opportunity to return to normal and to repair damage which has already taken place.

Acute Generalized Peritonitis: With the advent of potent chemotherapeutic agents, generalized peritonitis has become a problem of lesser magnitude than was formerly the case. Nonetheless, the morbidity and mortality rates are still uncomfortably high.

Over the past several months we have had the opportunity to follow a number of children and adults who have been admitted with this condition.[19] Appendiceal rupture has been the etiologic factor in the majority of instances, the rupture having occurred 24 or more hours prior to admission. All of these patients have received chemotherapy. Despite this, the majority who have received ACTH and cortisone have been critically ill prior to the institution of hormonal therapy.

The first such patient was a child of two and one-half years, admitted with a diagnosis of peritonitis resulting from appendicitis, rupture having occurred some days previously. The sequence of events over a period of 27 days is shown in figure 6. The essential facts appear to be as follows:

1. Chemotherapy at no time adequately controlled the local or systemic manifestations of the peritonitis.

2. ACTH in a dosage of 25 mg. every six hours resulted in complete disappearance of local and systemic signs and symptoms.

3. Discontinuance of ACTH resulted in prompt reappearance of local and systemic findings, despite continuance of chemotherapy.

4. At surgery, on the twentieth hospital day, evidence of widespread peritonitis with adhesions and localized pockets of pus was present. Slow convalescence ensued after surgery.

Subsequent patients have been placed on the following régime:

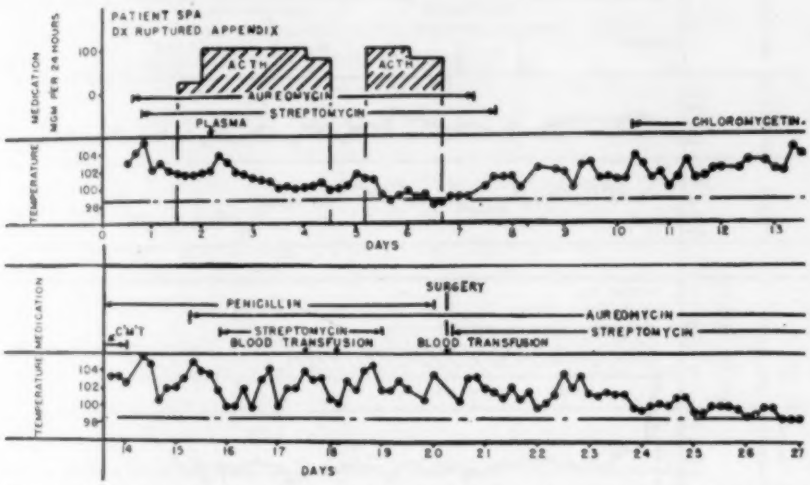

FIG. 6. Effect of ACTH (in conjunction with chemotherapy) upon a patient with severe generalized peritonitis. All toxic manifestations disappeared during ACTH administration, and reappeared when hormonal therapy was discontinued.

1. Chemotherapy plus ACTH and/or cortisone shortly after admission.

2. Surgery within 12 hours after the disappearance of local and systemic signs and symptoms.

3. Evacuation of all purulent material, removal of the appendix and closure without drainage, as in a simple appendectomy.

4. Continuation of chemotherapy and hormonal therapy for approximately a week.

The progress in two patients with peritonitis of comparable severity, one treated with chemotherapy alone and one with chemotherapy plus ACTH, is shown in figure 7. At surgery, the peritoneal cavity of the second patient was found to be filled with purulent material. Despite this, the parietal and visceral peritoneal surfaces were not friable or edematous. Convalescence and wound healing were completely uneventful, and he was discharged from the hospital on the ninth postoperative day.

The patient who received only chemotherapy had a significantly slower convalescence, associated with discomfort, vomiting, intermittent pyrexia and drainage from the incision.

It seems probable that the addition of ACTH and cortisone to chemotherapy in patients with generalized peritonitis will reduce both mortality and morbidity, and that it will eliminate the need for the prolonged Ochsner type of régime. It is probably rarely necessary to continue hormonal therapy for a period of more than a week in most instances.

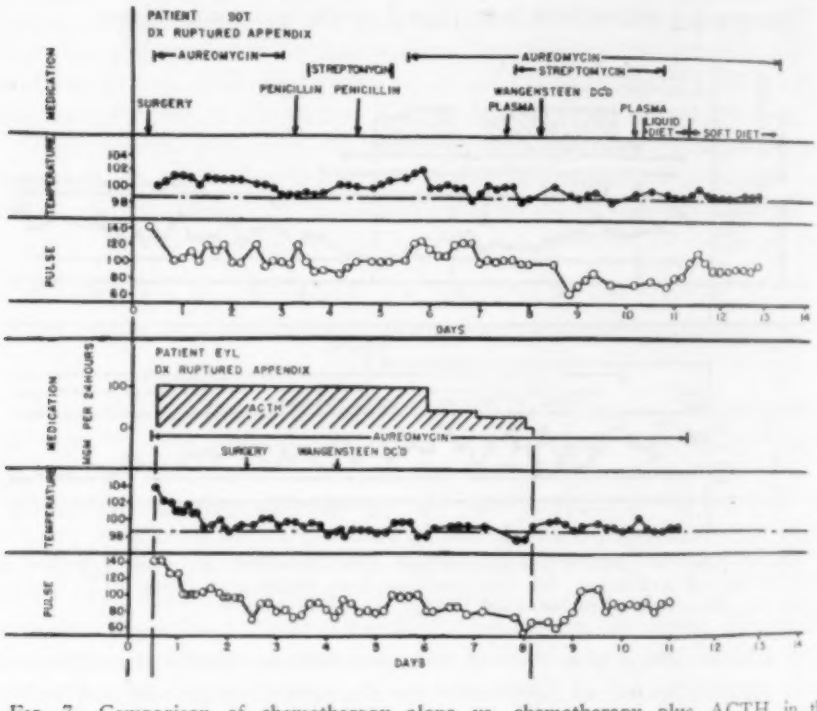

FIG. 7. Comparison of chemotherapy alone vs. chemotherapy plus ACTH in the management of generalized peritonitis. Morbidity appears to be significantly lessened in patients receiving combined therapy.

Acute Severe Systemic Infectious Processes of Known Etiology Which Fail to Respond Adequately to Chemotherapy: Relatively few observations are as yet available on the use of ACTH and cortisone as adjuncts to specific chemotherapeutic agents in infectious processes resulting from bacteria or other microörganisms. From the observations which are available, however, it appears that the hormones are of value in some of those individuals who fail to make an adequate response to properly administered chemotherapy.

Finland's observations concerning the use of ACTH in pneumococcus pneumonia have already been mentioned.[7] Chemotherapy alone will control

the majority of patients who have pneumococcus pneumonia. It is probable, however, that in some of those patients who fail to respond adequately to chemotherapy, particularly those in whom considerable debility was present before the onset of the infection, the administration of ACTH and/or cortisone will represent a life-saving procedure.

Two recent reports indicate that the addition of cortisone to chemotherapy in the management of typhoid fever results in more rapid response than is obtained with chemotherapy alone.[20a-b]

In our experience, the administration of ACTH to a child with severe meningococcemia which failed to respond adequately to chemotherapy appeared to be a life-saving procedure.

The possible value of ACTH-cortisone as an adjunct to antitoxin in the therapy of tetanus has already been mentioned.

It is to be emphasized that the administration of the hormones to patients with acute systemic infectious processes should be only as an *adjunct* to chemotherapy, *never as a substitute* for chemotherapy. Injudicious administration of the hormones to patients with severe systemic infections, without concomitant chemotherapy, can result in a masking of symptoms and progression of the infection to a point where chemotherapy will be ineffective!

Extensive Burns and Shock from Other Causes: As has been the case with most of the other conditions in which ACTH and cortisone have been alleged to be of great value, the report by Whitelaw [21] of their use in the management of patients with extensive burns was looked upon with understandable skepticism. The doubt is banished when one has an opportunity to observe the effects of the administration of these agents in patients with severe burns involving more than 60 per cent of the body surface. In many, perhaps in most of them, exudation, edema, shock and impairment of renal function are minimized to an impressive degree. It is frequently possible for these patients to take adequate amounts of food and fluid by mouth within 48 hours, and to become ambulatory in a remarkably short period of time. Those patients whom we have followed have impressed all observers by their lack of requirement for analgesic or narcotic medication.

Needless to say, all other standard measures for the management of burns should be utilized, *including the administration of adequate chemotherapy.* Hormonal therapy should be continued for a period of many weeks.

Acute, Severe, Localized Inflammatory Processes Which Fail to Respond Adequately to Other Therapy: Under this heading at the present time will be included only inflammatory conditions involving the eye. In no condition in which ACTH and cortisone have been used have the results been more impressive. Olson, Steffensen, Margulis, Smith and Whitney [22] reported their findings in patients with iritis, keratitis, chorioretinitis and iridocyclitis a year ago. Since then numerous reports have appeared.[23a-k] There is general agreement that the administration of ACTH and cortisone

systemically and of cortisone locally, either in the form of ointment or by subconjunctival injection, is of value in a wide variety of inflammatory conditions of the eye of known and unknown etiology.

Conditions in Which ACTH and Adrenal Steroids Are of Considerable Value

Under this heading will be included arbitrarily those conditions in which one may expect a prompt and impressive remission in the disease process in response to the administration of either or both hormones, a remission which will persist as long as medication continues, in which frequently the dosage of the agent may be progressively decreased over a variable period of time, and in which, in some instances, remission may persist when medication is discontinued after a suitable period of time. The following disease states appear to fall in this category: adrenogenital syndrome, allergic (hypersensitivity) syndromes, colitis (ulcerative), dermatomyositis, gout, hypoglycemia (idiopathic), pemphigus, Reiter's syndrome, rheumatoid arthritis and scleroderma.

Adrenogenital Syndrome: Wilkins, Lewis, Klein and Rosenberg [24] first reported that the administration of cortisone to patients with virilizing syndromes resulting from congenital hyperplasia produced a prompt fall in the excessive output of urinary 17-ketosteroids. This is presumably referable to inhibition of production of endogenous ACTH. It is still too early to know to what degree the clinical manifestations of the disease will regress during such therapy.

Allergic (Hypersensitivity) Syndromes: Following the demonstration by Thorn and his coworkers [16] of the fall in circulating eosinophils induced by ACTH and cortisone, it was natural that the effect of these agents upon the eosinophilia and upon the clinical manifestations of allergic patients should be determined. Some aspects of this problem have been commented upon earlier in this paper (see above). In a review paper, Segal and Herschfus [25] cover most of the pertinent literature up to the end of 1950.

The majority of investigators and clinicians agree that the administration of adequate amounts of ACTH and/or cortisone to patients with allergic manifestations results in prompt improvement, and frequently in complete disappearance of such manifestations. There is not general agreement as to the optimal duration of therapy. A number of statements appear in the literature to the effect that a relatively short course of therapy, in asthma and hay fever particularly, will result in a prolonged remission. This has not been our experience in the majority of such patients. Patients with long-standing bronchial asthma who are given initial intensive therapy, followed by gradual decrease in dosage over a period of weeks and months, seem to us to make much more satisfactory progress than do those who are treated intermittently. Further, it is our experience that the eosinophil level

in patients with allergic syndromes, particularly those who have had quite marked eosinophilia prior to therapy, serves as an excellent index of the proper dosage level to be maintained at any given time. We endeavor to maintain such patients at or below a level of 150 eosinophils per cubic millimeter of blood.

Beryllium Granulomatosis: Kennedy, Pare, Pump and Stanford [26] first recorded the use of ACTH in the treatment of beryllium granulomatosis. Significant improvement occurred and was maintained throughout the period of therapy. Dobson, Weaver and Lewis [27] report the progress of a patient with complicating tuberculosis.

Colitis (Idiopathic Ulcerative): DuToit and Bauer [28a-b] and subsequently others [29] have reported on the results of administration of ACTH and cortisone to patients with ulcerative colitis. From these reports, one may conclude that a certain number of patients with this disease will respond to hormonal therapy. It is our impression that the majority of such patients will show both symptomatic and objective improvement if adequate dosage is employed, but that long continued treatment is essential if the remission is to persist.

Dermatomyositis: There appears to be general agreement that dermatomyositis responds to the administration of ACTH and cortisone.[30a-c] Thorn,[31] in his evaluation of the ACTH-cortisone situation as of a year ago, felt that the addition of testosterone to ACTH-cortisone would result in significant improvement in muscle strength in these patients.

We have had the opportunity to follow several patients with this disease. One of them has been under continuous treatment for a period of more than one and one-half years. Her initial requirement was 40 mg. of ACTH daily; her present dosage level is approximately 3 to 4 mg. daily. Brief discontinuance of therapy on several occasions has resulted in prompt reappearance of signs and symptoms. On medication, she has been able to return to full time employment.

Gout: Wolfson and Cohn [32] consider in some detail the probable metabolic explanation for the clinical effects produced by ACTH and adrenal steroids in patients with gout.

They feel that a short course of ACTH therapy, followed by maintenance dosage of colchicine, represents a nearly optimal method of therapy for patients with gouty arthritis. Kuzell and Schaffarzich [33] noted significant improvement in five of seven patients. They agree that cortisone should be given only during the period of acute exacerbation. Friedlander [34] concurs in the general opinion that a short initial period of cortisone administration, followed by maintenance therapy with sodium salicylate, colchicine and low purine diet, represents a satisfactory procedure.

Our own experience is in accord with the opinions noted above.

Hypoglycemia (Idiopathic): McQuarrie, Ziegler, Bauer and Wright [35a-b] report that ACTH administered to children with this syndrome abolishes

the hypoglycemosis as long as the hormone is administered. Relatively small dosage appears to be adequate.

Pemphigus: Several patients with this syndrome have been observed by us during the past year.* One has been treated over a period of 11 months. Her clinical progress has been instructive:

Prior to the institution of ACTH therapy she had been hospitalized for nearly a year. Despite all therapy her course had been progressively downward. In May, 1950, more than 90 per cent of her skin surface was covered with characteristic lesions. Her nutrition was very poor. Eosinophil counts averaged approximately 16,000 per cu. mm.

She made an excellent and immediate response to ACTH. At all times her clinical status and eosinophil count were parallel. She was discharged from the hospital on no hormonal therapy after approximately two months of such treatment. Her eosinophil counts averaged 300 at this time, and her skin and mucous membranes were *nearly,* but not entirely, free of lesions.

Approximately one month after discontinuance of therapy she had a sudden fulminating exacerbation of her disease.

Porcine ACTH in amounts of more than 200 mg. daily, with the subsequent addition of 300 mg. of cortisone daily, accomplished nothing. The administration of beef ACTH, in a dosage of 80 mg. daily, resulted in a fall of circulating eosinophils from more than 4,000 to nearly zero in the space of 24 hours, with rapid resolution of all the skin lesions. Subsequently, the patient again became sensitive to porcine ACTH and to cortisone, and for a period of many months has been maintained on minute doses of medication with *complete freedom* from any lesions. At present she receives 3 mg. thrice weekly. In view of her previous recurrence we are loath to terminate medication completely.

Reports in the literature on the treatment of this condition [36a-b] agree as to the immediate response to hormonal therapy, but tend to be pessimistic about the likelihood of producing complete remission. We feel that there will be less indication for such pessimism if initial therapy is sufficient in amount to eradicate all lesions completely.

Reiter's Syndrome: Ogryzlo and Graham [37] report three patients with this condition, all of whom responded dramatically but relapsed promptly when ACTH or cortisone therapy was discontinued. They feel that the course of the disease was somewhat shortened by hormonal therapy. Our experience is limited to one patient, who responded to intensive therapy and promptly relapsed when the dosage was decreased.

Rheumatoid Arthritis: Only medical hermits could have failed to see Dr. Hench's "before and after" moving picture. Perhaps the majority of practicing physicians in this country have duplicated the results obtained by the Mayo group. Almost two score reports are already in the literature on the

* We are indebted to Dr. Julian Lunsford, Dr. Herman Allington, Dr. R. R. Allington and Dr. Gordon Lamb for the privilege of following some of these patients.

subject. Of the most recent, the paper by Hench, Slocumb, Polley and Kendall,[38] published in December, 1950, covers the more important points. They indicate that a program is currently under way in their institution designed to determine the optimal method for hormonal treatment of patients with this disease.

During the past two years we have observed more than 80 such patients. A few have been and are under intensive long-term study and treatment on the metabolic ward. From this experience our clinical impressions are as follows:

1. Nearly 100 per cent of arthritic patients show objective and subjective improvement when treated with ACTH and/or cortisone.
2. Initial therapy should be intensive enough to eliminate completely all evidence of joint inflammation. The dosage required is larger than in many other syndromes in which the hormones are effective.
3. Therapy should not be interrupted, but should be decreased gradually over a period of many months.
4. Limitation of salt and certain other dietary modifications, which will be discussed elsewhere, will lessen significantly the tendency to "toxic manifestations."

Other aspects of therapy in this disease will be discussed under the heading of "general considerations" (see below).

Scleroderma: Bayles, Stout, Stillman and Lever [39] reported improvement in this condition during ACTH therapy, with prompt relapse when therapy was discontinued. This is in accord with our own very limited experience.

Conditions in Which the Effects of ACTH-Cortisone Seem Highly Variable

Anorexia Nervosa: Thorn and his associates [14] state that "after administration of 40 mg. of ACTH daily in four divided doses to two such patients, a marked increase in appetite occurred at once." These investigators feel that prolonged therapy is a valuable adjunct to psychotherapy.

Prior to the availability of ACTH-cortisone in quantities sufficient for clinical application, we used combined testosterone-estrogen therapy in four patients with this syndrome, and noted significant increase in appetite and some improvement in emotional status.[40] Our experience with ACTH treatment is limited to one such patient. Short term therapy produced results comparable to those obtained with testosterone-estrogen.

Eclampsia: Gaton, Reid and Robey [41] reported that a combination of ACTH, cortisone and stilbestrol produced great improvement in two patients with severe toxemias of pregnancy.

Hematologic Disorders: The literature on the use of ACTH and adrenal steroids in disturbances of the hematopoietic system is already rather ex-

tensive. A portion of it has recently been reviewed editorially by Wintrobe.[42] Summarized very briefly, the consensus appears to be as follows: *Leukemia:* Many patients with acute lymphatic leukemia [43] respond rapidly in both a clinical and a hematologic sense. Prolonged remissions may result.

All other forms of leukemia [43a-f, 44a-f] show an unpredictable variability in response. Temporary or continued exacerbation of the disease may result during therapy. *Purpuras and "Hypersplenism":* Clinical and hematologic improvement has been reported.[45] *Hemolytic Syndromes:* Prompt inhibition of abnormal hemolysis may result in such patients.[46] *Agranulocytosis:* Rapid bone marrow regeneration has been reported.[47] *Myeloma:* Temporary subjective and objective improvement has been reported.[45a]

The rationale for the use of the hormones in the hematologic entities may be based upon the following:

(1) The "antitoxic" effects of the hormones (as in the case of agranulocytosis, the hemolytic syndromes, and perhaps other blood diseases as well).

(2) The stimulation of formation of granulocytes and platelets, and perhaps of red cells.

(3) The destruction of lymphocytes, monocytes and eosinophils.

Hodgkin's Disease: Three patients with Hodgkin's disease were given hormonal therapy by Stickney, Heck and Watkins.[43d] Little improvement occurred.

Three patients with the disease have been observed by us while under treatment. One patient became rapidly worse; the other two received little or no clinical benefit from therapy.

Hypoadrenocorticism (Functional): Thorn and his associates [14] believe that the diagnosis of *relative* adrenal cortical insufficiency may be made by determining the eosinophil response to ACTH administration, and, further, that "cortisone may be used with great advantage in the treatment of such patients."

We concur, with some reservations. In our experience, there is a small group of patients who are chronically tired, who have constant hypotension, and who respond sluggishly, but nonetheless surely, to ACTH administration. Such patients, placed on complete fast for a period of three or more days, will not develop hypoglycemic manifestations. Without exception, these individuals have been under constant emotional tension for prolonged periods of time. One could speculate as to the possible existence of an entity which might be given some such title as "functional suprahypophyseal hypoadrenocorticism." *Such speculation does not for a moment imply that every chronically tired, emotionally unstable individual* "has trouble with his glands." Even less does it suggest that psychoneurotics as a group will benefit from hormonal therapy.

Liver Damage (Acute and Chronic): For present purposes, no attempt will be made to divide liver disease into specific categories from the standpoint of etiology, since the observations in any one category are still fragmentary.

Thorn et al.[48a] reviewed the situation one year ago and concluded that the hormones would have a place in the management of hepatic disease. Flink and Williams [48b] noted relief of pruritus associated with a fall in blood bile acid concentration. Hanger [48c] believes such therapy to be of value.

We have administered large amounts of ACTH and cortisone to two patients with severe liver damage, one presumably viral in origin, the other probably referable to chemical intoxication. Brief improvement occurred in both patients, but each eventually died. Extensive hepatocellular destruction was found at autopsy. It is conceivable that the outcome would have been different had hormonal therapy been administered earlier in the disease.

Lupus Erythematosus Disseminata: Initial objective and subjective improvement has been noted in almost all such patients so far reported.[49] Our own experience agrees with this observation, but as yet we have observed no patient in whom complete clinical remission has been obtained. Convulsive seizures have occurred in two of four of our patients who have received initial intensive therapy. For this reason, it is our practice to begin therapy with small dosage of hormone, and to increase as rapidly as the clinical status of the patient permits. It has been suggested that the tendency to convulsive seizures in these patients is referable to potassium loss and sodium retention. It may, therefore, be well to institute a program of high potassium, low sodium intake, plus testosterone propionate administration *before* and during ACTH-cortisone therapy (see below).

Flood and Limarzi [50] report a decrease in the number of L. E. cells in the bone marrow of patients receiving hormonal therapy.

Periarteritis: Baggenstoss, Shick and Polley [51] reported on the clinical and subsequent pathologic evaluation of two patients suffering from periarteritis nodosa who were treated with cortisone. Impressive initial improvement was noted in both patients, but death subsequently occurred despite continued therapy. At autopsy, extensive infarction of numerous organs was found, apparently referable to complete healing of previously active arterial lesions.

We have followed only one patient with periarteritis during the course of intensive and relatively prolonged ACTH and cortisone therapy. This man appeared to have involvement of essentially his entire arterial system. During the early phase of therapy, he had complete subsidence of fever and marked increase in well being, and was able to resume a program of moderate activity for a period of several months. He eventually died from congestive heart failure, despite continued therapy. Necropsy unfortunately was not

performed, but it appears probable that the congestive failure resulted from progressive infarction plus continued hypertension.

It seems likely that patients with early forms of this disease may experience complete and prolonged remissions in response to adequate hormonal therapy. In advanced periarteritis, ACTH and cortisone probably should be administered initially in relatively small dosage to avoid too rapid healing of arterial lesions, with resultant infarct formation in major viscera.

Psoriasis: O'Leary, Montgomery, Brunsting and Kierland [52] report on the intermittent ACTH and cortisone therapy of a patient with psoriasis. Major improvement occurred during the period of therapy, with immediate relapse when therapy was discontinued. Verbal reports from other dermatologists are in accord with these observations. Two patients, followed by us for periods of more than four months, have shown immediate response to therapy. They have required relatively high dosage for continued improvement.

Renal Disease: The pathologic and physiologic classifications of diseases of the kidney have always been beset with difficulties. These same difficulties carry over when one attempts to evaluate the effects of ACTH and cortisone in the treatment of syndromes in which renal abnormalities are prominent. For purposes of description, renal disease will be considered under two categories:

1. *Acute and chronic nephritis with azotemia.* Keith, Power and Daugherty [53a] reported that the administration of cortisone to such patients increased azotemia and hyperpotassemia. Thorn, Merrill, Smith, Roche and Frawley [53b] felt that the evaluation of the effect of ACTH in patients with acute glomerulonephritis was impossible because of the tendency to spontaneous improvement. They state that in seven patients with subacute and chronic glomerulonephritis treated with ACTH and cortisone there was no evidence of any beneficial effect upon the renal disease. Burnett, Greer, Burrows, Sisson, Relman, Weinstein and Colburn [53c] felt that the net effect of cortisone administration to a patient with acute glomerulonephritis was harmful rather than otherwise.

2. *Nephrotic syndrome.* Farnsworth and her collaborators [54a] first reported the results obtained in response to the administration of ACTH and cortisone to patients with the so-called nephrotic syndrome. Several reports have since appeared in the literature. All appear to be in general agreement on the following points [54b–f]:

a. Patients with severe forms of the nephrotic syndrome (without azotemia) are entitled to a therapeutic trial of ACTH and cortisone.

b. Some patients during the period of therapy will have a major diuresis and a marked decrease or complete disappearance of proteinuria.

c. Others will have increased fluid retention during the period of hormonal administration, but a marked diuresis in association with decreased proteinuria when hormonal treatment is discontinued.

d. Some individuals with the nephrotic syndrome fail to have a diuresis or a decrease of proteinuria during or following ACTH or cortisone administration.

e. Extreme individual differences in electrolyte behavior during and following ACTH and cortisone administration are noted. It is therefore most essential that all patients so treated shall be followed from the standpoint of sodium, potassium and chloride blood levels and, if possible, in terms of sodium and potassium excretion. The administration or withholding of these minerals must be determined on an individual basis.

f. The present status of the entire problem is extremely confusing and extremely interesting.

The author and his associates are quite as confused and quite as interested as everyone else.

Rheumatic Fever: There is a real question as to whether rheumatic fever should properly be listed under the heading of "conditions in which the effects of ACTH and cortisone are highly variable" or "conditions in which ACTH and cortisone are of considerable value." It has purposely been placed in its present category to emphasize that much knowledge must still accrue before one can be sure of the proper rôle of ACTH and cortisone in the management of patients with rheumatic fever.

Massell and his co-workers, reporting at the First Clinical ACTH Conference [55a] and subsequently in the *New England Journal of Medicine*,[55b-c] were most optimistic in their evaluation of the results obtained in rheumatic fever patients. Barnes [55d] concluded that cortisone and ACTH can effectively suppress the acute manifestations of rheumatic fever, but stated that in "eight of 14 patients, one, several, or all of the acute manifestations of the disease reappeared when administration of the hormones was discontinued. These flares continued to reappear after subsequent resumption and omission of injections of the hormone until apparently the rheumatic state had reached the termination of its natural duration." Almost all reports appear to be in substantial agreement on the following points [56a-f]:

1. Nearly all patients suffering from an initial attack of acute rheumatic fever will experience prompt decrease or disappearance of signs and symptoms of the disease in response to adequate dosage of ACTH and cortisone.

2. Early discontinuance of therapy will result in prompt reappearance of signs and symptoms of the disease in most patients.

3. Therapeutic response in patients with rheumatic fever of long standing is much less favorable.

4. The danger of precipitation of acute heart failure in the early phases of hormonal therapy in patients with badly damaged hearts is always present. Such patients should receive small dosage of the hormones initially, plus mercurial diuretics and other indicated therapy, until the acute danger has passed.

Our own experience in the hormonal treatment of patients with this disease is limited, but is in complete accord with the above impressions. It seems probable that every individual in the early phase of an initial attack of severe rheumatic fever should have the benefit of hormonal therapy. How long such therapy should be continued is still unknown. It is our present practice to advise continuance of full therapeutic dosage for a period of two weeks, followed by gradual decrease in dosage over the following two weeks, with complete discontinuance of therapy in most patients at the end of that time. The nonspecific blocking effect of adrenal steroids is most apparent in this disease. Until such time as the fundamental etiologic factors of rheumatic fever are understood, it seems reasonable to believe that a significant amount of cardiac damage may be prevented by the judicious use of these agents.

Diseases in Which ACTH/Cortisone Should Be Used Only Under Controlled Investigative Conditions

Hypertension: Perera, Fleming, Pines and Crymble [57] observed the effect of cortisone in a dosage of 200 mg. daily for a period of one month in a woman with uncomplicated hypertensive vascular disease. They state that, following a preliminary rise, there was a small but definite decline in "resting" blood pressure while the patient was receiving the steroid. The occurrence of hypertension in patients with Cushing's syndrome, and the repeated demonstration of the tendency of ACTH and cortisone to produce hypertension in many patients, would provide very little basis for the belief that either hormone would be of value in the management of patients with essential hypertension. It is conceivable, however, that ACTH-cortisone therapy might have some beneficial effect upon the hypertension in some patients whose hypertensive disease is attributable to inflammatory changes in the arterial system or to an active nephritic process.

In hypertensive patients with other disease states which call for ACTH or cortisone therapy, the hormones must be used with great caution. In these patients it is mandatory that sodium intake be kept at extremely low levels during the period of therapy.

Neoplasms: The use of ACTH and cortisone in the treatment of the leukemias has already been considered. In other types of neoplastic processes, the situation at the present time defies any attempt at systematic analysis. Inhibition of tumor growth has been reported by some observers, and stimulation of such growth by others. At the present time, there appears to be no obvious histologic basis for such differences. Experimental work in animals is no more revealing.[58a-h]

Neurologic Diseases (Non-bacterial): With two exceptions, no attempt will be made to evaluate the reports already in the literature regarding the administration of ACTH and cortisone to patients with degenerative dis-

eases involving the central nervous system. Almost without exception they are pessimistic, but it is the feeling of the author that, in view of the time required for regeneration of nerve tissue, neither pessimism nor optimism is warranted until long-term, well controlled observations are available.[59a-c]

A recent report by Aronson, Douglas and Lewis [65] on the use of cortisone and ACTH in the treatment of two children with chorea indicates that little or no improvement resulted. In view of the relationship of this condition to rheumatic fever, and its ready reversibility in its early phases, it is probable that the reason for the failures was inadequate dosage.

The situation in regard to myasthenia gravis calls for considerable clarification. Millikan and Eaton [59a] report that, of five patients with very severe myasthenia gravis to whom ACTH or cortisone was administered, two had no improvement, one had slight transitory improvement, one had moderate transitory improvement, and one had marked transitory improvement after administration of the hormones had been completed.

Psychoses: Of historic interest is the observation that, during the period of initial evaluation of cortisone (prior to the demonstration of its clinical usefulness), Thorn was impressed by the lack of metabolic effects of the compound and equally impressed by the improvement in general energy and mental outlook, as well as in the electroencephalographic pattern of Addisonian patients who received the hormone. The accumulation of observations to date regarding the effects of ACTH and cortisone upon the psyche [60a-b] may be summarized as follows:

1. The majority of patients receiving either preparation experience an impressive degree of euphoria in association with decreased fatigability.
2. A certain number of patients become pathologically excitable.
3. A smaller group develop frank psychoses. It is almost axiomatic that serious mental disturbances develop only in individuals who have a history of emotional instability or of actual psychoses.
4. In almost all instances, the disturbance in the psyche disappears when hormonal administration is discontinued.

In our experience with the administration of these agents to more than 200 patients, we have seen all degrees of changes in the psyche. We are impressed with the observation that a number of patients during such therapy tend to have a release of inhibitions which at times can be desirable and at other times embarrassing or distressing. We are also most impressed with the decrease in sleep requirement which occurs in a large percentage of patients receiving ACTH in amounts in excess of 60 mg. daily, or of cortisone in dosage of more than 200 mg. daily. Many of these individuals find it impossible to sleep more than two to four hours out of the 24, and have no feeling of fatigue during their waking period; in fact, the majority are filled with energy and a desire to accomplish. One might speculate as to whether *spontaneous* differences in sleep requirement might be at least in part related to endogenous adrenocortical activity.

As in the case of organic disease of the nervous system, a very long period will be required before one will know whether ACTH and cortisone have any legitimate place in the routine clinical management of the psychoneurosis and the psychoses.

Syphilis: Turner and Hollander [61] observed marked changes in experimentally induced syphilomas in rabbits during ACTH and cortisone administration. These observations might suggest that in tertiary lues the combination of ACTH-cortisone with intensive chemotherapy might be more effective than chemotherapy alone.

Thyroid Disease: Reiss, Riggs, Thorn and Forsham [62a] reported that iodine uptake was diminished in patients receiving ACTH and cortisone. Hardy, Riegel and Erisman [62b] noted low protein-bound iodine levels in patients immediately following ACTH or cortisone therapy. These observations suggest that some adrenal steroids inhibit the production of thyrotrophin. Salassa [62c] reported no improvement in exophthalmos in three patients with Graves' disease but without definite evidence of hyperthyroidism.

In this clinic during the past year, two patients with acute thyroiditis, one of whom had severe exophthalmos, have received intensive ACTH and cortisone therapy. In both patients the evidence of acute inflammatory involvement of the gland subsided promptly. Exophthalmos, which was severe enough in one patient to give rise to the question of advisability of a Naffziger's operation, decreased in marked degree in direct relationship to ACTH and subsequently to combined therapy. To date, however, continued administration has been necessary to prevent its recurrence.

Tuberculosis: A number of reports have already appeared in the literature concerning the use of ACTH-cortisone in both human and experimental tuberculosis.[63a–j] There is general agreement that ACTH and cortisone are potentially highly dangerous agents in patients with active or arrested tuberculosis. There is as yet a lack of agreement as to whether the hormonal agents may have a place in the treatment of at least some types of clinical tuberculosis.

We are in thorough accord with the concept that ACTH and cortisone should *not* be used at the present time in the treatment of patients with tuberculosis (except under controlled experimental conditions), with the one exception noted below. It is our opinion, however, that ACTH and cortisone will eventually have a place in the treatment of tuberculosis in conjunction with chemotherapy. This statement is based upon work at present underway in this and affiliated institutions.

The hormones *do* have a place at the present time in the routine clinical management of tuberculous meningitis. Two patients so far have been treated in this clinic. One was becoming progressively worse despite chemotherapy, and the other was essentially moribund at the time ACTH therapy was begun. Both patients are clinically well, and have normal

spinal fluids at the time of this report. The effect of the hormones in this condition is probably two-fold: first, that of blocking the effect of the tuberculosis toxin, and second, that of breaking down the barriers which surround tubercle bacilli and thus making them more susceptible to the effects of chemotherapy. The need for intensive chemotherapy during and following hormonal therapy is obvious.

Conditions In Which ACTH-Cortisone Are Relatively or Absolutely Contraindicated

Adrenogenital Syndrome: This has been discussed previously. It is obvious that ACTH is contraindicated in a condition resulting from adrenocortical hyperplasia. Cortisone, on the other hand, is of major value.

Cushing's Syndrome: The reasons are obvious.

Cardiac Failure: This condition has been considered to some degree under the heading of rheumatic fever. The use of ACTH and cortisone in the presence of cardiac insufficiency calls for most careful clinical management, including the use of a sodium intake below 200 mg. per day, and the use of mercurial diuretics.

Diabetes: One obviously hesitates to use a diabetogenic agent in a patient with known diabetes. Again, if the associated condition is dangerous to life, and if there is good reason to believe that excellent therapeutic response to hormonal therapy will result, one may justifiably risk aggravation of the diabetic state.

In our experience with a few such patients, the degree of insulin resistance which may result during therapy can be disturbing. One should be prepared to administer large amounts intravenously as well as intramuscularly. It is also most essential that carbohydrate intake be kept low during the period of treatment.

Osteoporosis: If ACTH-cortisone therapy appears to be mandatory in a patient with osteoporosis, adequate dosage of testosterone and estrogen must be co-administered.

Peptic Ulcer: Perforation of peptic ulcer has occurred sufficiently often during the administration of ACTH and cortisone therapy to lead one to suspect that the association is not coincidental.[64a–d] In some instances, perforation has occurred in individuals with no previous ulcer history.

Perforation of a duodenal ulcer occurred in one of our patients during intensive therapy for an acute dermatomyositis. The perforation was not recognized for nearly 24 hours after its occurrence, because of the masking effect of the hormones. Extensive peritonitis was present at the time of surgery.

If hormonal therapy must be used in a patient with known or suspected ulcer, it is most advisable to use intensive "anti-ulcer therapy" during the period of treatment, as a prophylactic measure. The most important aspect

of such therapy is constant and complete neutralization of free hydrochloric acid in the stomach.

General Considerations

As has been previously emphasized in this paper, *ACTH and cortisone cure nothing*. One therefore administers either or both agents to patients suffering from acute or chronic diseases with the intent and expectation of producing a partial or complete remission in the clinical manifestations of the disease process, but without influencing the primary etiologic factor.

Dosage: The dosage situation in regard to ACTH is in a state of flux. Until very recently, the material has been given entirely as an aqueous solution by intramuscular injection. Using the hormone in this fashion, it has been necessary to administer it at intervals of six hours because of the short duration of action. During recent months, however, several groups of investigators, including Gordon, Wolfson, Thorn, Starr and their respective co-workers, as well as our own group, have evaluated the metabolic and clinical effects of ACTH administered intravenously, and of suspensions of ACTH injected intramuscularly. It appears probable that these two forms of administration will entirely supplant the intramuscular administration of aqueous solutions. Intravenous administration results in major economy, i.e., greater therapeutic effectiveness of a given dose, in a magnitude of several hundred per cent. Intramuscular administration of a suspension makes a single daily injection feasible, although the efficiency of a given 24 hour dose is not more than 70 per cent of the same amount administered as aqueous solution intramuscularly every six hours.

Since most of our present knowledge is based upon the aqueous, intramuscular, six-hour procedure, dosage will be discussed from this aspect. Suitable corrections may be made when the material is administered intravenously or as an oil suspension.

Cortisone is nearly or quite as effective by oral administration as by injection. Hence, except under special circumstances (e.g., subconjunctival administration in patients with ocular pathology; intramuscular administration in patients unable to take oral medication), oral administration of the total dose in four equal portions (after meals and at bedtime) may be considered the method of choice.

It appears probable that the dosage of these hormones, as well as of hormones in general, is much the same for children and adults, i.e., no modification on the basis of age or weight is indicated.

In the acute infectious conditions such as peritonitis, in which one administers the hormones in conjunction with adequate chemotherapy, the objective is to administer a dose of hormonal material which will induce a complete disappearance of the manifestations of the disease in the shortest possible period of time. If one uses ACTH, he should give no less than 25

mg. intramuscularly every four hours. If cortisone is to be used, adequate dosage will be not less than 300 mg. per 24 hours, given at three-hour intervals throughout the 24 hours. If both agents are to be administered, proportional amounts will be used. If within the first 24 hours major improvement in the clinical status of the individual is not observed in conjunction with a fall in eosinophil count to less than 25 cells per cu. mm. of blood, the dosage should be increased by 50 or 100 per cent. Hormone administration in these dosages is rarely continued for more than 10 days.

In the chronic conditions, we feel that the following program is advisable in the majority of instances:

Sufficient hormone should be administered initially to obliterate completely all evidence of activity of the disease state within the first few days.

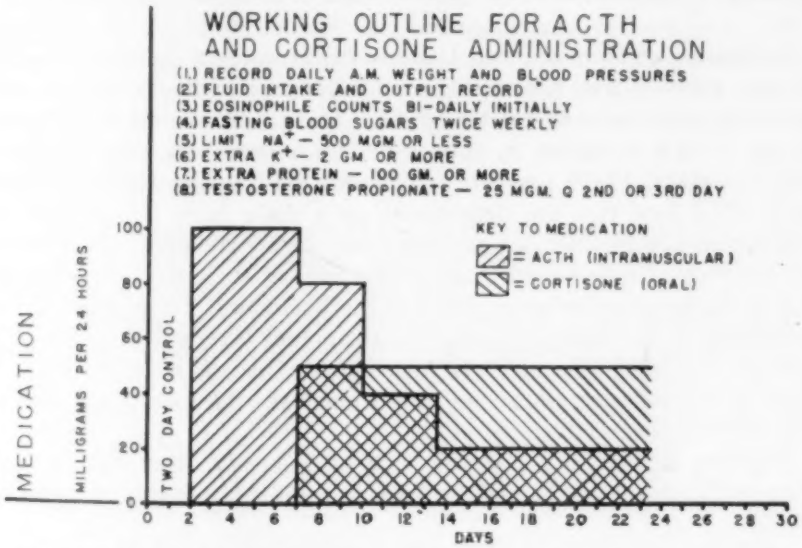

FIG. 8. Considerations regarding dosage, diet and general clinical management.

The dosage should then be reduced *gradually* over a period of many weeks and months, as warranted by the clinical status of the patient. Figure 8 shows the general plan of attack we have used for some time in the majority of patients with chronic disease states. It will be noted that such patients are initially treated with ACTH in a dosage of 25 mg. every six hours, after a control period of two or more days during which time the base line values for blood sugar, eosinophils, weight and blood pressure are obtained. Subsequently, the dosage of ACTH is decreased and cortisone is co-administered. Such co-administration in patients who require prolonged treatment is much more physiologic than the administration of either alone, inasmuch as either excessive stimulation (from ACTH), or the production of adrenal atrophy (from prolonged cortisone administration) is undesirable.

Diet, Potassium, Testosterone: The majority of patients receiving these hormones will catabolize excessive amounts of protein tissue and excrete excessive amounts of potassium. They will also retain undue amounts of sodium and water, unless suitable measures are taken to avoid these undesirable effects. Therefore, as shown in figure 8, these patients receive a diet high in protein and low in sodium, and containing supplemental amounts of potassium. They also receive testosterone propionate in an amount sufficient to inhibit completely the protein catabolic effect of the ACTH-cortisone. The clinical effects obtained are equally as good, and in some instances better, when testosterone is co-administered. In female patients receiving testosterone propionate, one must be careful to avoid excessive masculinizing effects. Fortunately, most evidences of masculinization are reversible if administration of the hormones is not continued for too long a period.

Evaluation of Desirable and Undesirable Hormonal Effects: It is preferable that patients who are to receive ACTH and cortisone shall be standardized initially under hospital auspices. During the period of standardization, as shown in figure 8, four objective criteria are always followed, namely: weight, blood pressure, circulating eosinophils and fasting blood sugar. The first two are determined on a daily basis. Eosinophils and blood sugars are checked two or three times during the first week, and thereafter as often as may be indicated. The level of the circulating eosinophils gives one a good index of response to the hormones. In many conditions, particularly in the allergic states, the eosinophil level will mirror very accurately the clinical response. In patients with diseases characterized by elevation of the sedimentation rate, this should also be followed as a routine index of therapeutic effectiveness.

Needless to say, in conditions such as leukemia, liver disease, etc., in which special tests are in order, these also will be followed in appropriate fashion.

Evidences of excessive fluid accumulation (rapid weight gain, edema, excessive rounding of the face), with or without hypertension, call for a decrease in sodium intake to a level below 300 mg. per 24 hours. To accomplish this and still maintain a high protein intake, a desalted, reconstituted milk preparation such as "Lonalac" is of great help. The cation exchange resins may also be of considerable value.

A rapid or progressive rise in fasting blood sugar levels will raise the question as to the propriety of continuation of hormonal therapy. Fortunately such a situation seldom arises. It is our impression that the use of a diet containing essentially no concentrated carbohydrate will lessen the likelihood of occurrence of hyperglycemia in patients receiving large amounts of ACTH-cortisone over prolonged periods of time.

There are, of course, exceptions to the above general program. In our experience, patients with lupus erythematosus may be extremely intolerant

of the initial administration of large amounts of hormone. We therefore routinely begin therapy in such individuals with small dosage, and increase as rapidly as their tolerance permits. The majority of such individuals have no circulating eosinophils, hence there is obviously no point in attempting to evaluate the eosinophil level as an index of effectiveness of therapy.

Any attempt to indulge in specific directions for the therapeutic administration of agents which have as broad a physiologic spectrum as these hormones must be hedged with ifs and buts. As in the case of any potent drug, the judgment of the attending physician is the most essential ingredient of the prescription.

Summary and Conclusions

This report marks the end of the second year of the clinical availability and application of adrenocorticotropic hormone and of cortisone. There appears to be little question that these agents have changed and will continue to change the character of medical practice to quite as great a degree as have the chemotherapeutic agents. Their present place in clinical medicine may be summarized with a few maxims which at the present time appear to be well substantiated.

1. ACTH and cortisone have no inhibitory effect upon bacterial growth.
2. They do exert a polyvalent antitoxic effect, in some way protecting multiple body cells against multiple toxins.
3. In infectious or potentially infectious states, it is essential that hormonal administration be combined with highly adequate antibacterial therapy.
4. ACTH and cortisone can produce undesirable metabolic effects. Many and possibly all of these effects can be prevented by appropriate measures.
5. The greatest potential hazard attendant upon ACTH-cortisone administration lies in the masking of the signs and symptoms of advanced and advancing pathology. This must be kept in mind constantly!
6. Patients with chronic disease states should not be started on therapy unless they are financially able to continue such therapy for months and years.

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No reference is made in this bibliography to papers presented at the Second Clinical ACTH Conference, held December, 1950, inasmuch as the complete papers were not available for review. These papers have just become available at the time of submission of this report. (Proceedings of the Second Clinical ACTH Conference, John R. Mote, M.D., Editor, 1951, The Blakiston Company.)

THE FUNCTIONAL INTERRELATIONSHIP OF THE ANTERIOR PITUITARY AND THE ADRENAL CORTEX *

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THE size and the secretory activity of the adrenal cortex are controlled to a major extent by the adrenocorticotropic hormone (ACTH) of the anterior pituitary. The anterior pituitary adjusts its output of ACTH to meet the physiologic "needs" of the organism for cortical hormones. This paper is a review of some of the laboratory and clinical observations bearing upon this interrelationship. Some of the illustrations are drawn from my own laboratory data and experiences.

1. CONTROL OF ADRENAL CORTEX SIZE AND REGENERATION

The fact that hypophysectomy causes atrophy of the adrenal cortex was first demonstrated by Allen [1] and Smith [2] in studies on amphibia. Allen [3] also showed that this and other disabilities arising from hypophysectomy in the amphibia can be repaired by pituitary transplants. Smith and Smith [4] found that the intraperitoneal injection of extracts of the anterior lobe of bovine hypophysis in the hypophysectomized tadpole repairs the atrophic adrenal cortex and other deficiencies. In the first studies on mammals, Smith [5] demonstrated that hypophysectomy in the rat is followed by atrophy of the adrenal cortex, and that daily implants of anterior pituitary tissue prevent cortical atrophy. The partial separation of ACTH from the other hormones of anterior pituitary tissue was accomplished by Collip, Anderson and Thomson.[6] Subsequent studies led to the isolation of ACTH in apparently homogeneous form.[7, 8]

As reviewed by Tepperman, Engel and Long,[9] two additional facts were soon established. First, removal of one adrenal gland is followed by compensatory hypertrophy of the remaining adrenal cortex, but this does not occur in the absence of the anterior pituitary. Second, any type of stress to which laboratory animals are subjected caused adrenal cortical hypertrophy. This response is abolished by removal of the anterior pituitary.

In 1929, I initiated a series of studies on transplantation of the adrenal cortex of the rat which eventually led to a new set of facts. We, and others, found that a transplanted (autogenous) adrenal cortex will not regenerate in the presence of an intact adrenal gland. This principle was discovered by Halstead [10] in studies of parathyroid grafts in the dog. Similarly, a unilaterally enucleated adrenal gland does not regenerate cortical tissue in

* Presented at the Thirty-second Annual Session of the American College of Physicians, St. Louis, Mo., April 11, 1951.

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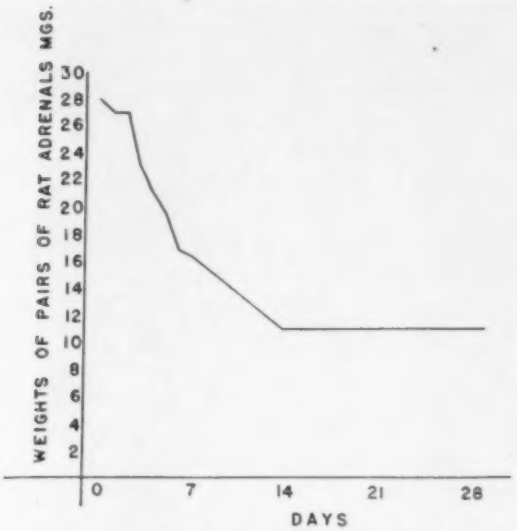


FIG. 1. Compensatory atrophy of the adrenal cortices in the male rat induced by the oral administration (drinking water) of 10 c.c. of beef adrenal extract daily. Average weights of pairs of adrenal glands. Five rats are represented at each point.

the presence of an intact adrenal, although regeneration ensues rapidly when the contralateral gland is completely removed or when enucleation is done bilaterally. The enucleated adrenal cortex will not regenerate in the hypophysectomized animal. We found that it is possible to suppress cortical regeneration almost completely by the administration of large amounts of adrenal cortex extracts. As a result of these studies, we were encouraged to study the effect of large doses of adrenal cortex extracts upon the intact adrenal gland. The oral or parenteral administration of large amounts of

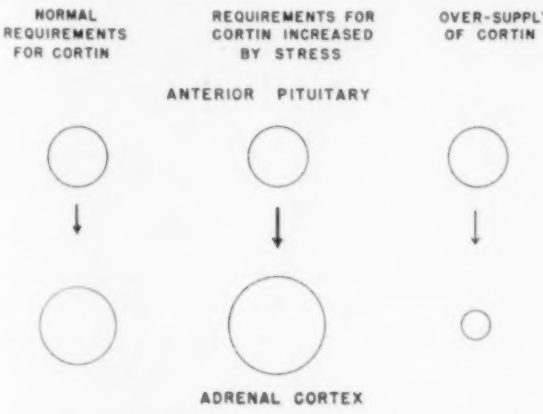
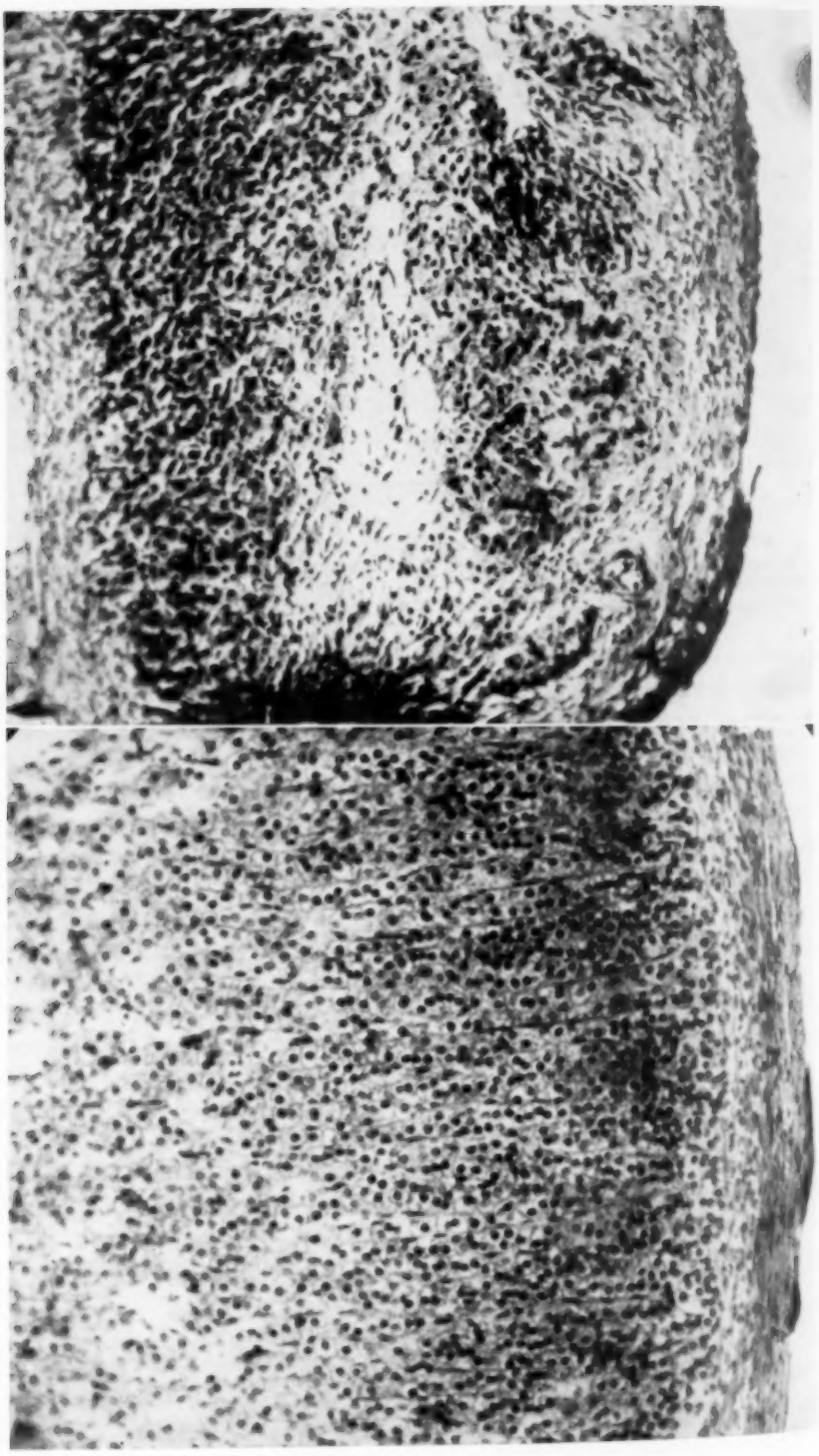


FIG. 2. Diagram of the general functional interrelationship between the anterior pituitary and the adrenal cortex.



beef adrenal extract caused cortical atrophy almost as extensive as is caused by hypophysectomy. This suppression is illustrated in figure 1. Corticosterone, 11-dehydrocorticosterone, 17-hydroxycorticosterone, cortisone and, to a lesser extent, 11-desoxycorticosterone also cause compensatory atrophy of the adrenal cortices. This atrophy is reversible. When overdosage is stopped, the adrenal cortices regain their normal size. When ACTH was administered simultaneously with an excess of adrenal cortex extract, compensatory atrophy of the cortices was prevented. Moreover, when hypophysectomized rats were given a uniform intake of ACTH in amounts sufficient to prevent adrenal cortical atrophy, the additional administration of large amounts of adrenal cortex extracts failed to affect the size of the cortices.

In parallel studies, it was first shown [11] in my laboratory that the adrenal cortical hyperplasia induced by stress could be suppressed by the administration of large amounts of adrenal cortex extract.

It therefore became possible in 1936–1937 to broaden our concept of anterior pituitary-adrenal cortex relationship. Not only does the stimulus for adrenal cortex maintenance and for hypertrophy during stress arise from the anterior pituitary but, by some direct or indirect means, the anterior pituitary is also sensitive to an excess of adrenal cortical hormones and is able to inhibit its output of ACTH accordingly. This general relationship is shown in the diagram of figure 2. At the time this concept was first stated,[12] one line of evidence remained incomplete. As noted above, the enucleated adrenal cortex will not regenerate in either the hypophysectomized rat or a rat having one intact adrenal gland. It was believed that regeneration of the adrenal cortex was controlled by ACTH, but when an attempt was made to stimulate the regeneration of the enucleated adrenal cortex by the intermittent injection of ACTH in the hypophysectomized rat, the results were negative. We have recently resolved this question. When ACTH is administered by continuous injection to either hypophysectomized rats or rats having one adrenal gland intact, the enucleated adrenal gland regenerates rapidly. This is illustrated in figure 3. Our studies on control of adrenal cortex regeneration in the rat have recently been reviewed.[13]

I recall the keen interest shown by the late Dr. E. J. Kepler, of the Mayo Clinic when I first described our laboratory observations on compensatory atrophy of the adrenal cortex. He exclaimed, "Now there is an observation by a physiologist which makes sense to a clinician!" He went on to say that patients having adrenal cortical tumors commonly show extensive atrophy of the contralateral gland. It is now known [14] that removal of the

FIG. 3. (*above*) Enucleated adrenal, 21 days; hypophysectomized rat. ×190. No regeneration has occurred; in fact, the parenchymal cells are more atrophic than in the freshly enucleated adrenal. (*below*) Enucleated adrenal from hypophysectomized male rat given ACTH by continuous injection for 21 days. ×190. Good regeneration has occurred uniformly around the gland.

hyperfunctioning tumor in such patients is followed by restoration of the atrophic cortex to normal functional activity. Dr. Kepler's kindly interest in my laboratory studies provided a welcome stimulus to continue research on the consequences of experimental hypercorticalism. Kepler was a great clinical investigator, whose keen insight into the experiments performed by nature on man pointed the way for many of us whose experience was confined to the laboratory.

2. Chemical Changes in the Adrenal Cortex Induced by ACTH

The general concept of anterior pituitary response to adrenal cortical insufficiency and excess has been fully supported by the more recent application of the elegant technics introduced by Dr. George Sayers and his associates.[15] Fluctuations in the secretory activity of the adrenal cortex are associated with changes in the concentration of certain chemical constituents of the gland. Under resting conditions, about 5 per cent of the wet weight of the adrenal cortex is cholesterol. Either the administration of exogenous ACTH or the increased secretion of ACTH during stress causes depletion of the cholesterol content of the adrenal cortex. In the absence of the anterior pituitary, stress fails to cause a fall in adrenal cholesterol. The literature has been reviewed by Sayers et al.[16] There is a great deal of indirect evidence to support the hypothesis that cholesterol may be a precursor of the adrenal cortical steroids.

Increased adrenocortical activity is associated with a reduction in the ascorbic acid content of the gland.[17] The quantitative relationship between the dose of exogenous ACTH and the extent of fall in adrenal ascorbic acid provides a sensitive test for the bio-assay of ACTH and for measuring rapid changes in adrenal cortical activity during stress. In general, the changes in concentration of cholesterol and of ascorbic acid in response to ACTH run parallel, but in the rat the decrease in ascorbic acid is more rapid than in cholesterol, and during the recovery phase the ascorbic acid is restored more rapidly than in the cholesterol.

It has been shown by Gemzell[18] that the administration of ACTH increases the rate of turnover of phosphorus in the adrenal cortex of the rat.

In our earlier studies,[11] using weights of adrenal glands as an index of adrenal cortex response, we found evidence that the discharge of ACTH and activation of the adrenal cortex could occur within six to 12 hours. The idea that the response could occur so rapidly met with some resistance from other investigators in the field. We, in turn, have been amazed by the results obtained when chemical changes in the adrenal cortex are used as indices of speed of response. It has been shown that the anterior pituitary can discharge ACTH within a few seconds following a stress,[19] and that the adrenal cortex can respond to ACTH within a few seconds.[20] These changes occur prior to demonstrable changes in morphology. Still unanswered is the question as to how the effect of ACTH upon the secretory

activity of the adrenal cortex and its effect upon adrenal size are causally related.

3. Questions Relating to the Nature of ACTH

In 1943, Li, Evans and Simpson [7] and Sayers, White and Long [8] reported the isolation of an apparently homogeneous protein with a molecular weight of about 20,000 from the pituitary glands of the sheep and hog, respectively, which was considered to represent the natural form of ACTH. It has now been found that this protein can be chemically degraded into smaller molecules which possess the biologic properties of ACTH. Chemically, these preparations represent a mixture of polypeptides. Li [21] has reviewed the recent progress in this field and has given the name "ACTIDES" to the active polypeptide mixture. At the present time, there is no agreement among investigators in the field as to whether the naturally occurring hormone is a large protein molecule which can be degraded into smaller active parts, or whether the hormone is a relatively small molecule which is adsorbed upon or otherwise associated with a protein carrier. In terms of the available tests for the purity of proteins, ACTH behaves as a single substance. Although ACTIDE is highly active in causing the discharge of ascorbic acid in the adrenal cortex, it has appeared to be relatively ineffective in stimulating adrenal cortex repair in the hypophysectomized rat when it is administered by intermittent injection. During the past few months, I have collaborated with Dr. C. H. Li in comparing the biologic activity of ACTIDE and ACTH given by continuous injection to normal rats. Under the conditions of our experiments, ACTIDE stimulates adrenal cortical hyperplasia and signs of hypercorticalism almost as effectively as does ACTH. The clinical effectiveness of ACTIDE in causing remission of arthritis in man has been demonstrated.[22, 23]

The question as to whether the anterior pituitary secretes more than one ACTH is unsettled. Selye [24] and Albright, Forbes and Bartter [25] have summarized evidence relating to this question. Only one principle has been isolated. Most, if not all, of adrenal cortical functions known to be controlled by the anterior pituitary have been shown to be affected by the known preparations of ACTH. Although the burden of proof lies with the protagonists of the multi-ACTH hypothesis, it would be unsound to conclude that the unitarian concept has been proved.

4. Factors other than ACTH Which Affect Adrenal Cortical Function

There is uniform agreement that the adrenal cortex has some residual function in the hypophysectomized animal. In the rat, the zona glomerulosa is affected by hypophysectomy to a lesser extent than are the inner zones of the cortex. The hypophysectomized rat does not show the abnormalities in electrolyte balance which characterize the adrenally insufficient rat.

Swann [26] and Greep and Deane [27] have postulated that the glomerulosa functions independently of the anterior pituitary and secretes a hormone which regulates electrolyte balance. This autonomy concept derives support from the observations of Deane, Shaw and Greep [28] that the cytology of the zona glomerulosa of hypophysectomized rats can be affected by the level of sodium, potassium and chloride in the diet and by the administration of 11-desoxycorticosterone. The following observations weaken this hypothesis: Hypopituitarism in man is characterized by abnormalities in electrolyte metabolism; ACTH does affect electrolyte balance in man; the effect of 11-desoxycorticosterone upon the adrenal cortex is not limited to the zona glomerulosa; Selye and Stone [29] have claimed that the zona glomerulosa does not escape the effects of hypophysectomy in the rat; and, finally the enucleated adrenal cortex, having only the capsule and a layer of glomerulosa cells remaining, is still responsive to ACTH, and the regenerated cortex sustains the normality of the animal in respect to organic metabolism.

There is no doubt that certain stimuli can affect the structure of the adrenal cortex independently of ACTH. Miller and Riddle [30] found that insulin causes hypertrophy of the adrenal cortex in the hypophysectomized pigeon. Certain steroids and growth hormone affect the histology of the adrenal cortex of the hypophysectomized rat. The effect of ACTH upon the structure of the adrenal cortex can also be conditioned by certain dietary factors, by other hormones and by a number of stresses. The data relative to this problem have been reviewed by Selye and Stone.[29] The full significance of these observations cannot yet be appraised.

5. Mechanism of Control of ACTH Release

The adrenocorticotropic activity of the anterior pituitary represents a major control over the secretory activity of the adrenal cortex. What controls the anterior pituitary? The following considerations relate to this question.

A. The anterior pituitary may be sensitive to either the level of adrenal cortical hormones in the blood or to the metabolic consequences of their action. There is abundant evidence that the anterior pituitary secretes more ACTH into the blood during adrenal cortical insufficiency and suppresses its output of ACTH in the presence of an excess of adrenal cortical hormone. Why are increased amounts of cortical hormones required during stress? Either it may be necessary to attain a higher concentration of the cortical hormones in the body fluids during stress, or stress may cause an increase in the "utilization" of cortical hormones so that a compensatory increase in secretory activity is required to keep a uniform level of hormones in the blood. Either or both of these possibilities may be true. If a higher concentration of cortical hormones in the body fluids is required during stress, it seems unlikely that this could be achieved if the anterior pituitary is sensitive

only to the concentration of cortical hormones per se. It would be more logical to assume that the anterior pituitary is sensitive to some metabolic consequences of cortical hormone action.

B. The rapidity with which the anterior pituitary responds to stress and its anatomic relationship to the central nervous system suggest the possibility that there may be nervous control over the release of ACTH. However, there is general agreement that the infundibulum can be sectioned without preventing the release of ACTH during stress. Hume and Wittenstein [31] reported indirect evidence that lesions in the paraventricular nucleus of the hypothalamus of the dog can abolish the release of ACTH during stress. Since the neural connections between the hypothalamus and pituitary of the dog can be destroyed without interfering with the response of the anterior pituitary to stress, it was suggested by Hume and Wittenstein that the hypothalamus may secrete a humoral agent which activates the anterior pituitary to release ACTH. Harris and DeGroot [32] have reported that lesions in the hypothalamus of the rabbit abolish the lymphopenic response to emotional stimuli, and have drawn the conclusion that the secretion of ACTH is under the neural control of the hypothalamus. In the rat,[33, 34] transplants of the anterior pituitary to the anterior chamber of the eye are capable of releasing ACTH in response to stress. These experiments prove that ACTH release is independent, in part at least, of its normal neural connections and is sensitive to some change in the fluids which reach it.

C. Long [35] has suggested that the activation of the sympathetic nervous system, and the consequent release of epinephrine during stress, may play a specific rôle in stimulating the rapid release of ACTH during stress. Long has emphasized, however, that the adrenosympathetic system is not the only mechanism involved in ACTH regulation. Epinephrine is known to be discharged during certain types of stress. The administration of exogenous epinephrine causes a release of ACTH by the anterior pituitary. In the rat, interruption of the sympathetic pathways involved in the reflex secretion of epinephrine prevents the eosinopenic response to certain types of stress. Injection of epinephrine into the anterior chamber of the eye causes the discharge of ACTH from a transplant of anterior pituitary tissue in that site.[36] The fact that epinephrine can elicit a release of ACTH by the anterior pituitary is not in doubt, but it has been questioned whether it plays a specific physiologic rôle in controlling anterior pituitary activity. Sayers and Sayers [17] have shown that the injection of adrenal cortex extract just prior to the injection of epinephrine in the rat blocks the release of ACTH. This experiment adds some support to the view that epinephrine serves as a nonspecific stress.

In my opinion, it has been established beyond reasonable doubt that the anterior pituitary responds to humoral factors in adjusting its secretion of ACTH. It seems probable that these mechanisms function, in part at least, independently of the nervous system. It is simpler to explain the

immediate discharge of ACTH during acute stress as a response to epinephrine or a neurohumoral principle from the hypothalamus than to explain the chronic effects of prolonged stress or compensatory atrophy of the adrenal cortices on such a basis. The possibility that two or more general mechanisms are involved in the regulation of the adrenocorticotropic activity of the anterior pituitary cannot be discounted at present. Studies having to do with this general problem have been reviewed in detail by Sayers.[37]

6. The Metabolic Consequences of the Anterior Pituitary-Adrenal Cortex Response During Stress

In our laboratories, we have obtained indirect evidence that the adrenal cortices of the normal adult male rat secrete the activity equivalent of 3 to 5 c.c. daily of beef adrenal extract under nonstress conditions. Two criteria have been applied.

A. When the mildly diabetic male rat on a constant food-intake is adrenalectomized, there is a striking decrease in the level of urinary glucose. From 3 to 4 c.c. of cortical extract are required to restore the glycosuria to its preadrenalectomy level.

B. As noted above,[13] the presence of one intact adrenal inhibits the regeneration of a contralateral enucleated adrenal in an otherwise normal male rat. In similar rats having one enucleated adrenal with the other adrenal removed, an average of 5 c.c. daily of beef adrenal extract is required to inhibit regeneration of the enucleated adrenal as effectively as does the presence of one intact adrenal gland.[38]

During a severe stress, the adrenalectomized rat requires much greater amounts of adrenal cortex extract or of steroids to sustain optimal resistance. We[39] have studied the requirement for cortical extract in adrenalectomized rats subjected to faradic stimulation of the gastrocnemius muscle. When the hormone was given by continuous intravenous injection, 20 c.c. per 24 hours of beef adrenal extract were required to sustain a normal output of work. In unpublished studies, it was shown that when cortisone acetate was given by subcutaneous injection at the beginning of work and again six hours later, 5 mg. per 24 hours were required to support the maximal output of work that could be attained with this steroid. When the free alcohol of cortisone was administered by continuous intravenous injection, 3 to 4 mg. per 24 hours were required to support the maximal output of work that could be attained with this steroid. Cortisone alone does not provide complete support for the adrenally insufficient rat in any dose.

When amounts of exogenous cortical extract or of cortisone such as are required to maintain optimal resistance to severe stress are administered to either intact or adrenalectomized rats under nonstress conditions, signs of hypercorticalism ensue. The animal develops a negative nitrogen and potassium balance and loses weight; there is extensive regression of the thymus

and a lesser response in the other lymphoid organs; there are marked changes in certain blood elements; the animal may develop a glycosuria; its resistance to infection is lowered, and some animals develop gross pathology such as renal lesions and ulcers in the pyloric portion of the stomach. Many of these changes from normal have not yet been clearly defined.

In further studies, we have explored the dose-response relationship for ACTH. As previously shown by us,[13] ACTH elicits its greatest effect upon

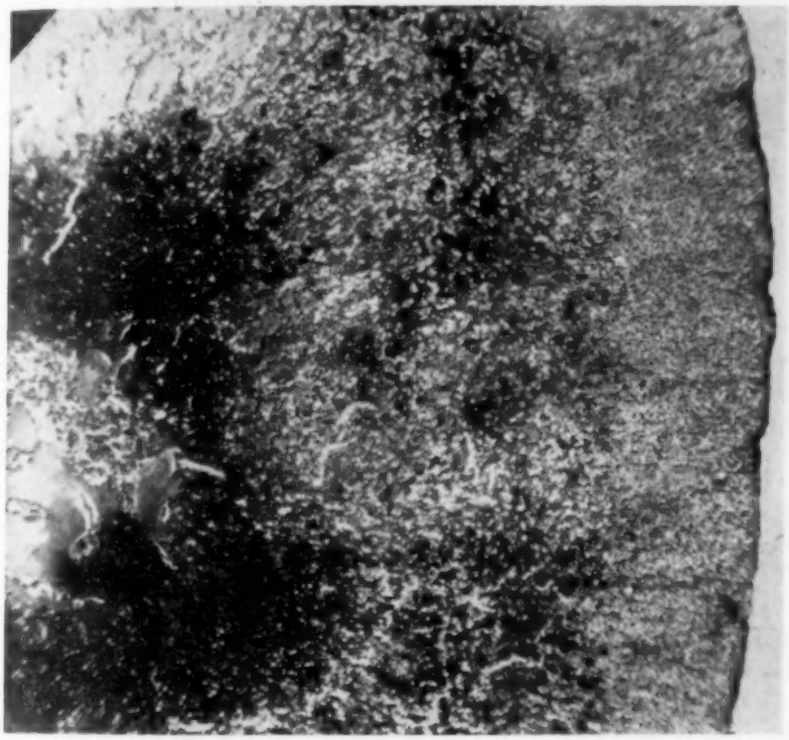


FIG. 4. Intact adrenal of a male rat given ACTH by continuous injection for 21 days. ×49. This section extends into the medulla. Around the periphery is a rim of normal cortex. From there into the medulla is an area of necrosis, accompanied by hemorrhage and pools of stagnant blood.

the size and secretory activity of the adrenal cortex when it is administered by continuous injection. This observation, that ACTH has its greatest biologic effects when administered by continuous injection, has been confirmed in clinical investigations.[40, 41] Using an apparently homogeneous form of ACTH, prepared by Professor C. H. Li, we (Ingle, Baker and Li, unpublished data) have found that 6 mg. daily given by continuous subcutaneous injection to normal male rats cause enormous hyperplasia of the adrenal cortices. We have found single adrenal glands weighing up to 286

mg. Upon gross inspection, these glands appeared hemorrhagic. Actually they probably represent vascular stasis. Pools of blood were found within areas of necrotic medullary and cortical tissue. The pathologic changes were confined to the medulla and the inner zones of the cortex. The outer zone of the cortex remained intact and viable. A section of such a gland is shown in figure 4. The metabolic and tissue changes described above as representing experimental hypercorticalism were markedly accentuated, so that these animals were brought to death by the overproduction of steroids from their own adrenal glands within three weeks. These observations demonstrate that the latent secretory capacity of the adrenal cortices of the rat is very great, much greater than is needed to meet the requirements for hormones during severe stress. We then set about determining the amount of cortisone required to duplicate the metabolic and tissue changes which can be caused by maximal stimulation of the rat's own adrenal cortices. Approximately 10 mg. daily of cortisone acetate were required. In other words, we have indirect evidence that the adrenal cortices of the adult male rat have the latent capacity to secrete an average activity equivalent of 10 mg. of cortisone acetate daily. Since the adrenal cortices apparently have a latent capacity for a much greater response than is known to be required, we are inclined to doubt that adrenal cortical exhaustion can be caused by exposure of the rat to stress. We suspect, but have not proved, that the pathologic changes occurring in the adrenal glands of rats subjected to the continuous injection of ACTH may simulate the pathologic changes seen in animals and in patients following severe stresses such as burns and fulminating infections; i.e., the hemorrhagic adrenal of the Waterhouse-Friderichsen syndrome may be caused in major part by the outpouring of ACTH in response to severe uncompensated stress.

Let us now return to the question, What are the metabolic consequences of the anterior pituitary-adrenal cortex system activation during stress? We have carried out four experiments in our laboratories which relate to this question and provide a basis for a tentative answer.

A. Large doses of estrogen cause stimulation of the adrenal cortex via the discharge of ACTH by the anterior pituitary. Estrogens cause exacerbation of glycosuria in the partially depancreatized force-fed rat. This response does not occur in the adrenalectomized-depancreatized rat. Activation of the adrenal cortex by the administration of exogenous ACTH, adrenal cortex extracts or 11-oxygenated steroids causes exacerbation of glycosuria in the partially depancreatized rat. On the basis of these observations, it was postulated that activation of the adrenal cortex mediates the effect of estrogen upon glycosuria. The following experiment [42] was carried out: Partially depancreatized rats, which were without spontaneous glycosuria, developed glycosuria during the injection of 0.1 mg. daily of diethylstilbestrol, and the glycosuria disappeared when the injections were stopped. The animals were then adrenalectomized and treated with a sub-

diabetogenic amount (3 c.c. daily) of adrenal cortex extract. Glycosuria developed when diethylstilbestrol was injected and disappeared when the injections were stopped. When the animals were maintained by treatment with either 11-desoxycorticosterone acetate or by drinking 0.9 per cent sodium chloride, the diabetogenic effect of the estrogen was either slight or absent. The data are summarized in figure 5. The study was repeated [43] on adrenalectomized, hypophysectomized, partially depancreatized rats maintained on subdiabetogenic amounts of adrenal cortical and anterior pituitary extracts. The administration of diethylstilbestrol caused hyperglycemia and glycosuria in all of the test animals which were without glycosuria during the control periods, and in animals having spontaneous glycosuria it became more severe when the estrogen was administered. These data show that the estrogen has a diabetogenic effect which is not mediated by a change

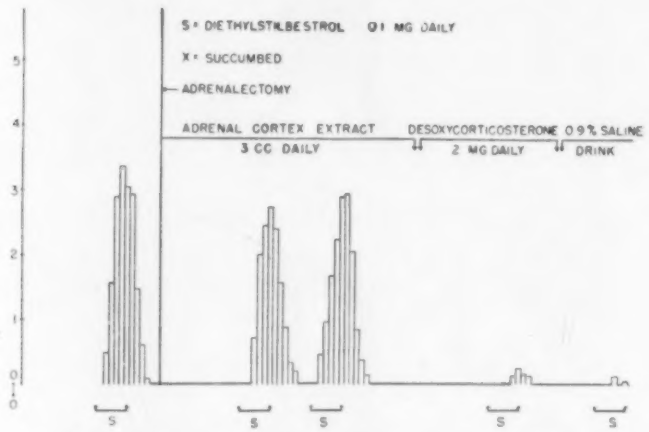


FIG. 5. The diabetogenic effect of diethylstilbestrol before and after adrenalectomy of the partially depancreatized rat as influenced by the nature of the replacement therapy. Taken from Ingle.[42]

in the secretory activity of the adrenal cortex, but that the presence of cortical hormones is essential for the support of this metabolic response.

B. A similar problem has to do with the effect of estrogen upon the growth of hair. The systemic administration of large doses of estrogen over a period of several weeks suppresses the growth of hair in rats. Hair growth can be similarly inhibited by large doses of adrenal cortex extracts, 11-oxygenated steroids or of ACTH. It is known that large doses of estrogen cause stimulation of the adrenal cortex via ACTH. Hair growth is accelerated by adrenalectomy in the rat and is not inhibited by the administration of estrogen in the adrenally insufficient rat. A test was made of the hypothesis that the hair-growth inhibiting effect of the estrogen was mediated by an increase in the secretory activity of the adrenal cortices. Here again, it was shown [44] that the cortical hormones play a supporting rôle, for

when the adrenal glands of rats were removed and the animals treated with cortical extract, the hair-growth inhibiting effect of the estrogen was sustained. Illustrative data are shown in figure 6.

C. The same principle is illustrated by our study [45] on the relationship of the post-stress rise in nitrogen excretion to adrenal cortex function. Following fractures, burns, surgery, infections and trauma, laboratory animals and humans usually develop a negative nitrogen balance. Since the secretory activity of the adrenal cortices is increased during stress, and since

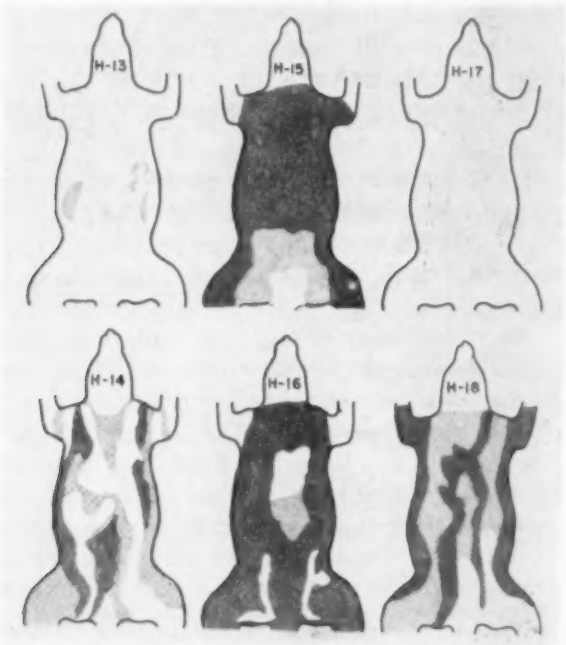


FIG. 6. Drawings of hair pattern grown during the fourth week following operation. H-13, sham adrenalectomy, estrogen; H-14, sham adrenalectomy, control; H-15, adrenally insufficient, estrogen; H-16, adrenally insufficient control; H-17, ACE-treated adrenalectomized, estrogen; H-18, ACE treated adrenalectomized control. Taken from Ingle and Baker.[44]

large doses of either adrenal cortex extracts or of the 11-oxygenated steroids cause an increased nitrogen loss, it has been postulated that the post-stress negative nitrogen balance is caused by activation of the adrenal cortices to secrete more hormone. In our experiments, the urinary non-protein-nitrogen of adrenalectomized and sham-operated, force-fed male rats was studied following fracture of the hind legs. In the first experiment (figure 7), saline was the only therapy used. There was no significant rise in urinary non-protein-nitrogen following the breaking of the tibia and knee-joint of one leg of the adrenalectomized rats, but a significant rise occurred in the non-

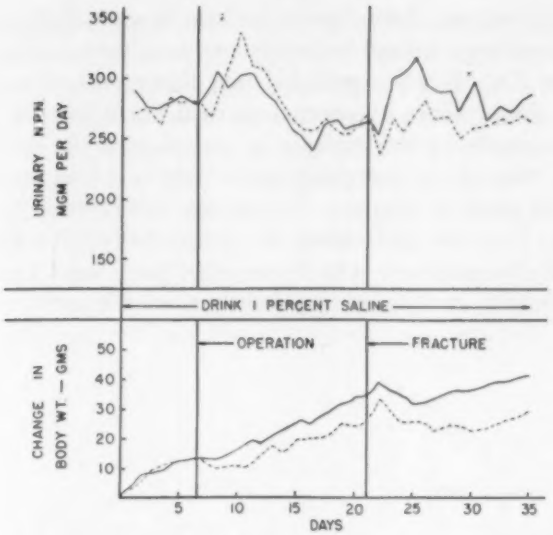


FIG. 7. The effect of operation and of multiple fractures of one leg on the urinary non-protein-nitrogen of six pairs of sham-operated (·———) and saline-treated, adrenalectomized (x - - - -) rats. Taken from Ingle, Ward and Kuizenga.[45]

adrenalectomized rats. In the second experiment (figure 8), the adrenalectomized rats were treated with 4 c.c. of cortical extract daily. Following fractures, there was a marked rise in urinary non-protein-nitrogen in all of the rats. The third experiment was identical with the second except that

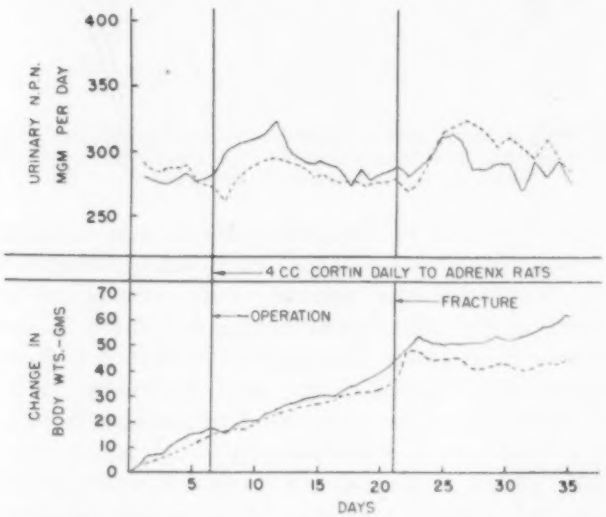


FIG. 8. The effect of operation and of multiple fractures of one leg on the urinary non-protein-nitrogen of six pairs of sham-operated (·———) and ACE-treated (x - - - -) adrenalectomized rats. Taken from Ingle, Ward and Kuizenga.[45]

the tibia, knee-joint and femur were broken in each back leg. The post-fracture rise in urinary non-protein-nitrogen was very striking in all of the animals (figure 9). It was concluded that this metabolic response to fractures requires the presence of adrenal cortical hormones for support but is not caused specifically by the increase in secretion of the cortical hormones.

D. On the basis of the foregoing experiments, it was postulated that the consequences of cortical hormone action are determined by the extent of "need" for the hormone as related to the quantity of hormone involved. Thus a quantity of hormone which exceeds "need" and causes hypercorticalism under resting conditions may barely meet the increased "need" dur-

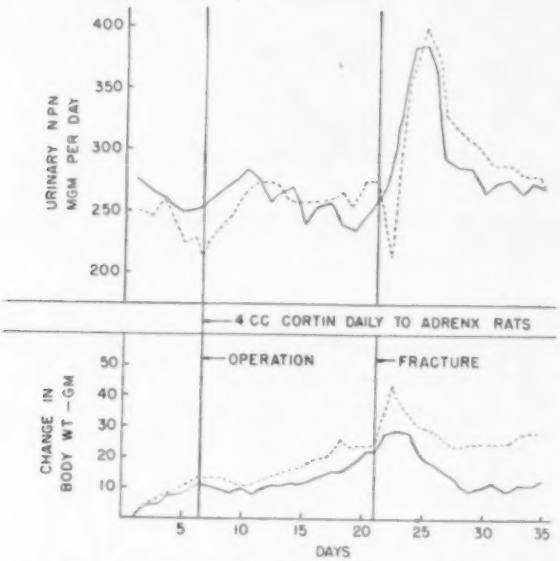


FIG. 9. The effect of operation and of multiple fractures of two legs on the urinary non-protein-nitrogen of six pairs of sham-operated (·———) and ACE-treated (x- - - -) adrenalectomized rats. Taken from Ingle, Ward and Kuizenga.[45]

ing severe stress, and under the latter condition fails to cause signs of hypercorticalism. A partial test for this hypothesis was based upon the following considerations: It is known that adrenal cortex extracts and 11-oxygenated steroids are diabetogenic when given in excess, and that stimulation of the adrenal cortices by large doses of exogenous ACTH is diabetogenic. Diabetes is ameliorated by removal of the adrenal cortices. Would any non-specific stress cause exacerbation of the diabetic state in the partially depancreatized rat via the ACTH activation of the adrenal cortices? We have studied the effect of only a few forms of stress in the partially depancreatized rat, but the results have been uniform. There is some decrease in the glycosuria, rather than exacerbation. The responses of adrenalectomized and

nonadrenalectomized diabetic rats have been compared in respect to the effect of a stress upon the level of glycosuria.[46] Male rats were made mildly diabetic by partial pancreatectomy and were force-fed a medium carbohydrate diet. Fifteen rats were adrenalectomized and treated with adrenal cortex extracts in amounts which sustained the preadrenalectomy level of glycosuria. An equal number of nonadrenalectomized rats were studied in parallel. The subcutaneous injection of solutions of 1.5 per cent formaldehyde, in doses of 0.25, 0.5 and 1 c.c. twice daily for seven days, five rats per dose level, caused some decrease in the glycosuria of the nonadrenalectomized rats and a much more striking decrease in the glycosuria of the adrenalectomized rats. When the injections were stopped, the glycosuria

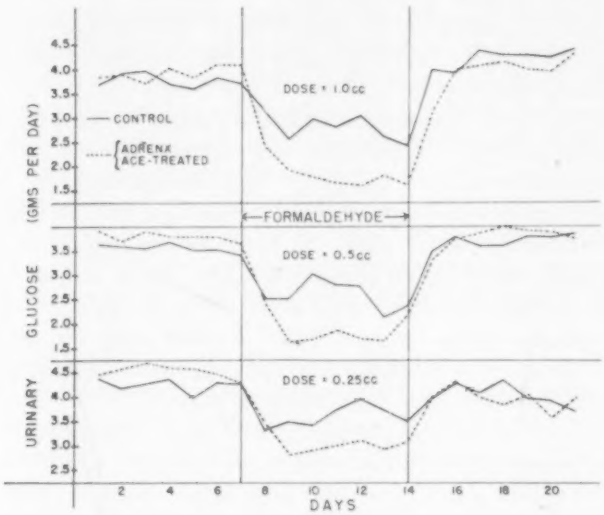


FIG. 10. Effects of injections of formaldehyde on glycosuria of depancreatized rats and of depancreatized-adrenalectomized rats treated with ACE. Each average is based upon five rats. Taken from Ingle and Nezamis.[46]

was reëstablished at its preinjection level. The data are shown in figure 10. It seems probable that the increased output of cortical hormones during the stress did have a positive effect upon the level of urinary glucose, in that it tended to prevent the marked decrease in glycosuria which occurred in the adrenalectomized rats. Those adrenalectomized rats which were on a fixed intake of cortical extract—an amount which represented full replacement under nonstress conditions—became adrenally insufficient during the increased need for more hormone, and the glycosuria fell sharply, as is characteristic of adrenal insufficiency. These data support the concept that the increased secretory activity of the adrenal cortices during stress tends to maintain homeostasis rather than to cause hypercorticalism.

Comment

This concept, that ACTH and the hormones of its target organ, the adrenal cortex, play a supporting rôle rather than a prepotent regulatory rôle in metabolic adjustments, is a hypothesis only. In addition to the bits of evidence which I interpret as offering support, the concept represents a reaction of my negativistic nature to the growing list of metabolic processes which the adrenal cortex is said to regulate. I did not originate the hypothesis. It is of uncertain parenthood, and I am among the few who have adopted it and have helped it to grow. Grollman [47] expressed essentially the same idea 15 years ago. Professor F. C. Mann, of the Mayo Foundation, held such a view as the result of pioneer studies on the physiology of the adrenal cortex more than 30 years ago.

It is unsafe to generalize in any field of science and especially so in endocrinology, although it has been done without signs of trepidation. We have studied only one species and but a few forms of stress. It is known that such stresses as infections and fractures cause exacerbation of diabetes mellitus in some patients. How does this response in man relate to changes in adrenal cortex function? Gordon [48] has summarized the evidence that the adrenal cortical hormones may play an etiologic rôle in diabetes mellitus in man. To consider other signs of hypercorticalism, it is established [49] that the increased secretion of cortical hormones is a major factor causing regression of lymphoid tissue and a decrease in blood eosinophils and lymphocytes during acute stress. Yet I believe that, for many metabolic adjustments, the anterior pituitary-adrenal cortex response has a supporting rôle rather than an obligatory regulatory action.

Selye [24] has observed the damaging effects of experimental hypercorticalism under special experimental conditions (unilateral nephrectomy, high-sodium, high-protein diet), and has postulated that the hormones of the adrenal cortex play a major etiologic rôle in many human diseases, which he has called "adaptation diseases." This concept is of great importance. If it is true, it will represent the greatest advance in the understanding of disease since the introduction of the germ theory. There is no doubt that an intact anterior pituitary-adrenal cortex axis is essential for the manifestation of certain diseases. Diabetes mellitus and hypertension are examples. Consider experimental diabetes as produced by pancreatectomy. The primary cause of the diabetic state is insulin deficiency, yet this diabetic state is ameliorated by removal of the adrenal cortices. Similarly, experimental hypertension can be caused by renal ischemia. The exciting cause of the hypertension lies in the kidney, yet blood pressure fails to normal or below when the adrenal cortices are removed. The experimental stresses which cause "adaptation diseases" in laboratory animals fail to do so in the adrenally insufficient animal. This is one of the major points supporting Selye's concept that an over-production or imbalance of the hormones of the adrenal cortex causes disease. The possibility that, here again, the response of the adrenal to stress simply supports the manifestation of damage rather

than playing the primary causative rôle has not been ruled out by any experiments yet published.

The following inexact analogy proves nothing but may serve to clarify my meaning. Consider an automobile (organism) whose speed (primary consequences of cortical hormone action) is kept constant by a mechanical governor (anterior pituitary). When the load (stress) is increased, the fuel supply (cortical hormones) must undergo an increase in order to keep the speed constant. Under usual conditions, the response of the governor serves to maintain normality under load. A weakened mechanism (unilateral nephrectomy) meeting additional obstacles (high sodium, high protein diet) is much more likely to wreck ("adaptation diseases") if it sustains a constant speed than is a similar automobile which is caused to run slowly or stall by restriction of its fuel supply. Nothing is assumed to be wrong with the operation of the governor, but it plays an essential, though not the primary, causative rôle in the resulting damage. Perhaps if the secretory activity of the adrenal cortex were controlled by the higher cerebral centers, an individual with diabetes or hypertension could take cognizance of the situation and voluntarily reduce the secretory activity of his adrenal cortices so that his disease would be ameliorated to some extent. A very wise man might be able to avoid situations of increased "need" for cortical hormones and guide the activity of his adrenal cortices successfully, but for most of us it would be a dangerous responsibility and a poor substitute for the "wisdom of the body."

It seems improbable to me that our present lines of research on the function of the adrenal cortical hormones will reveal the fundamental mechanisms of action. We have been observing and listing the overt signs of a sequence of events initiated by the primary biochemical and biophysical reactions into which the steroids themselves enter. If we can define the primary actions of the cortical hormones, the elucidation of their rôle in the cause and treatment of disease should be accomplished in due time.

Finally, I refer to a recent paper in which Sayers [50] has reviewed in much greater detail the functional interrelationship of the adrenal cortex and anterior pituitary and its rôle in the stress response. This paper has been both stimulating and comforting to me, for Sayers, too, has abandoned efforts to explain the functions of the cortical hormones in terms of the multitude of signs of their action. His characterization of their actions as "ubiquitous" seems necessary from the evidence that these hormones affect the functions of all of the cells of the body. This characterization does not, as he says, explain the rôle of the adrenal cortex but rather focuses our attention on the gap in our knowledge.

Summary

Changes in the morphology and secretory activity of the adrenal cortex are regulated in major part by the adrenocorticotropic hormone (ACTH) of the anterior pituitary. The adrenal cortex retains a residual function in

the absence of ACTH, and certain hormones and other stimuli have limited effects upon the morphology of the adrenal cortex independently of ACTH.

Only one ACTH principle has been proved to exist, although others have been postulated. ACTH has been isolated as a crystalline protein which behaves as a single substance according to the available criteria for testing the purity of a protein, although its purity is the subject of debate. ACTH has been degraded or dissociated into a mixture of polypeptides (ACTIDES) which retain the biologic properties of ACTH. It has been established that ACTH activity can be exhibited by one or more polypeptides.

The anterior pituitary is sensitive to the "needs" of the organism for adrenal cortical hormones and releases increased amounts of ACTH during any type of stress, so that increased secretory activity and hyperplasia of the adrenal cortices ensue. In the presence of an excess of exogenous cortical hormones, the anterior pituitary suppresses its release of ACTH so that compensatory atrophy of the adrenal cortices results.

The anterior pituitary is regulated, in part at least, by humoral factors transmitted to it through the blood. It may be sensitive to the level of cortical hormones per se, or to the metabolic consequences of cortical hormone action. In addition, there is evidence that the hypothalamus may have some rôle in controlling the release of ACTH by either nervous or neurohumoral mechanisms. Another hypothesis indicates a possible rôle for epinephrine in stimulating the release of ACTH, especially during acute stress which activates the sympathetic nervous system.

Evidence is reviewed to support the hypothesis that the response of the anterior pituitary-adrenal cortex axis during stress plays a homeostatic rôle and does not represent the exciting cause for many of the metabolic responses to stress. The hormones of the adrenal cortex are essential for the full-blown manifestation of some metabolic responses to stress. As a corollary, it is suggested that the apparent relationship of adrenal cortical function to the manifestation of certain diseases is based upon a rôle of essentiality for the cortical hormones, rather than representing primary causative agents. This is discussed briefly in relationship to Selye's concept of the "adaptation diseases."

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MENINGO-ENCEPHALITIS DUE TO BRUCELLOSIS WITH THE REPORT OF A CASE IN WHICH *B. ABORTUS* WAS RECOVERED FROM THE CEREBROSPINAL FLUID, AND A REVIEW OF THE LITERATURE*

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Meningo-encephalitis as a Manifestation of Brucellosis

The difficulty of establishing a diagnosis of brucellosis in many suspected cases and the great variability in the disease itself have made the pathogenesis of this infection in humans notoriously unsuited to critical study. The lack of any reliable treatment has further obscured an adequate understanding of the clinical manifestations attributed to the so-called "chronic" phases of this disease, which conceivably may be complicated or modified at any time by the development of any other complaint to which man is subject. The formation of a satisfactory concept of central nervous system involvement in brucellosis appears to present no exception to these difficulties. Reports on this rare complication, though few in number, have been more numerous in the foreign literature than in our own, and certain clinicians abroad have been sufficiently impressed by its frequency not only to attempt classification of cases into separate neurologic syndromes but also to suggest the possible existence of "neurotropic" and "meningotropic" strains of the organism.[1, 2, 3] In this country, reports have been largely confined to the description of isolated cases where the diagnosis seemed probable and, in rare instances, where it was established by recovery of the organism from the spinal fluid.

The purpose of this paper is to describe another case of meningo-encephalitis in which a Brucella organism was recovered from the cerebrospinal fluid, to review the clinical manifestations and laboratory findings associated with this manifestation of brucellosis through a consideration of the available literature, and to reëmphasize the apparent value of minor modifications in certain laboratory procedures in establishing the diagnosis.

Case Report

An incoherent, disoriented and ataxic 39 year old white male mechanic was admitted to the psychiatric service of the McCook Memorial Hospital in Hartford, Connecticut, on June 25, 1946. Eventual reconstruction of the past history revealed that he had lived in various rural communities of New Hampshire and Vermont until the age of 16. Except for an episode of "pleurisy with pneumonia" lasting about two weeks at the age of eight, and an attack of "tonsillitis" complicated by "convulsions" at nine, his health during childhood had been excellent. At 16 he went to

* Received for publication August 16, 1949.
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work as a mechanic. At this time he began to suffer from severe periodic headaches occurring at two to three month intervals. For 12 to 14 hours he would feel as if "the top of my head was being blown off." The attacks were accompanied but not preceded by dark spots before his eyes, occasionally by epigastric pain, and rarely by vomiting, sometimes self-induced. There was no family history of migraine or epilepsy. He never sought medication and was always able to "sleep off" the pain. He was a good mechanic and worked steadily during the 18 years prior to coming to Hartford. Heavy spree drinking, however, was usually in order over the weekends.

Though he had drunk raw milk from childhood, all milk consumed subsequent to taking up residence in Hartford presumably was pasteurized. He settled here in January, 1942, and started to work in a local garage, assuming the heavy truck repair jobs out of preference. At this time the attacks of headache began to occur approximately every two to three weeks. Their frequency was appreciably reduced when he started sleeping with his head elevated on two pillows. On occasion he also noted mild ataxia in the dark, a tendency to walk with a wider base, toe-stubbing on the level, and moderate fatigue of his arms and legs at the end of the day, often associated with bilateral tremor of the hands which subsided after a few hours of rest. During this period he was drinking fairly heavily. His appetite, however, remained excellent and his weight constant at about 135 pounds. On April 8, 1942, he was admitted in a state of acute alcoholism to the Hartford Hospital. Because of a blood pressure ranging from 140 to 170 mm. of mercury systolic and 85 to 110 diastolic, and the history of recent vague neurologic complaints, both of these aspects of the case were investigated. The hypertension did not prove a consistent finding, and at the time of discharge was considered "neurogenic" in origin. The neurologic examination was negative save for slight relative nerve deafness on the left. A lumbar puncture revealed an initial pressure of 120 mm. of cerebrospinal fluid, which fell to 80 following the removal of 10 c.c. of clear fluid. No cells were found. The protein content was 32 mg. per cent; the Kline and Hinton were negative and the colloidal gold curve was flat. A complete urinalysis, a blood non-protein-nitrogen determination, a phenolsulfonphthalein test, intravenous pyelograms and roentgenograms of the skull and chest were all within normal limits. The red blood cell count was moderately reduced, to 3,500,000, with a hemoglobin content (Sahli) of 12 gm.

Following discharge from the Hartford Hospital he returned to work. Although the headaches and previously mild neuromuscular symptoms occurred from time to time throughout the next two years, he recognized no new complaints until early in 1944. During this interval his habits had remained the same except for marked curtailment of week-end drinking, on the assumption that this might be related to his symptomatology. However, from 1944 to 1946 increasing fatigability became the major symptom. While retiring at midnight had been his habit for many years, he found the evenings increasingly shortened by fatigue until he was glad to go to bed immediately after supper. Insomnia of a mixed type began to occur with increasing frequency. At the garage, first by preference and later by assignment, he gradually shifted from heavy to light work.

Early in the spring of 1946 he noticed difficulty crawling from under cars and required more and more use of his arms in assisting himself to an upright position. On several occasions when stepping out of a bus, he was unable to support himself and fell down. During the month prior to admission progressive deafness developed, more noticeable in the right ear than the left, and transient lapses of memory occurred. Several times, on returning from work in the evening, he got off the bus, took the wrong turn and walked for a short distance before recognizing his mistake. A week prior to admission he developed a constant generalized headache, similar in character and location to those previously described but more severe and accompanied by pain and stiffness of the neck and legs. The day before admission, while on the

way to work, he is said to have fallen down and had a "fit." He was taken home by a friend and put to bed. The following morning the patient's wife noted that he was confused, walked unsteadily and with great difficulty, expressed himself incoherently and did not know what to say or do. On the afternoon of the same day, June 25, 1946, he was sent alone in an ambulance to the McCook Memorial Hospital.

For simplicity in presentation, certain clinical and laboratory aspects of the patient's hospital course and immediate subsequent follow-ups have been graphically presented in figure 1.

The first period of hospitalization in the McCook Memorial Hospital extended from June 25 to July 17. On admission he was ataxic, confused and disoriented, and responded incoherently. Although his sensorial disturbances cleared rapidly over the first five days, leaving only a residual memory loss for recent events and a mild degree of mental retardation, the initial moderate nuchal rigidity and strongly positive Kernig's subsided only very gradually over the next three weeks and never became entirely negative. A variable degree of fever was present throughout. The general physical examination was remarkable only in an initial blood pressure of 174 mm. Hg systolic and 110 mm. diastolic. The neurologic examination, except for the defects in cerebration and signs of meningeal irritation noted above, revealed only bilateral nerve deafness, more marked on the left; weakness of all the leg muscles, most pronounced in the extensors of the thighs, and absence of all deep reflexes in the lower extremities. Cranial nerve function, with the exception of the eighth, was intact. There was no nystagmus or vertigo. Motor function in the upper extremities and trunk appeared unimpaired. The deep reflexes of the upper extremities were all present and considered of normal intensity. All abdominal reflexes were absent, though the cremasteric reflex was present bilaterally. Pain and touch sensation and temperature differentiation, as well as position sense, were all grossly normal. There was no evidence of cerebellar dysfunction. The Babinski and Hoffmann reflexes were absent. Routine laboratory procedures, including complete blood, urine and stool examinations, were all within normal limits. Spinal fluid studies revealed normal pressure, moderate pleocytosis with a preponderance of lymphocytes, evidence of periodic subarachnoid bleeding with xanthochromia, increased protein concentration and negative smears and cultures. The latter were incubated aerobically, anaerobically, under increased carbon dioxide tension, and on a variety of media, including Sabouraud's. An acid-fast smear from a pedicle on one occasion was negative, and a guinea pig inoculated with some of this same fluid showed no disease when autopsied at the end of six weeks. Complement fixation tests for mumps and lymphocytic choriomeningitis were negative, as were the blood and spinal fluid Wassermanns. The colloidal gold curve was consistent with an increase in the protein content of the cerebrospinal fluid. Other examinations, including blood cultures and roentgenograms of the chest, skull, teeth, accessory nasal sinuses, cervical, dorsal and lumbar spine, pelvis and both lower extremities, were all within normal limits. An electrocardiogram showed mild T wave abnormalities but presented no diagnostic pattern.

On July 11, when the patient was transferred to the ward medical service, he was able to walk to the lavatory. The strength of his legs had improved both subjectively and to gross testing, but his gait was still unsteady and was performed on a broader base, though without demonstrable loss of position sense. No deep tendon reflexes in the lower extremities could be elicited. Because of the persistent low grade fever, blood for routine agglutination was drawn on July 15, and was reported on July 18 as positive only for Brucella, with a 4 plus flocculation out to a dilution of 1:640. No greater dilutions were made. The next night he went to bed feeling as well as at any time since admission. The following morning at 6:15 he was found on the floor by his bed, unresponsive and staring at the ceiling. There

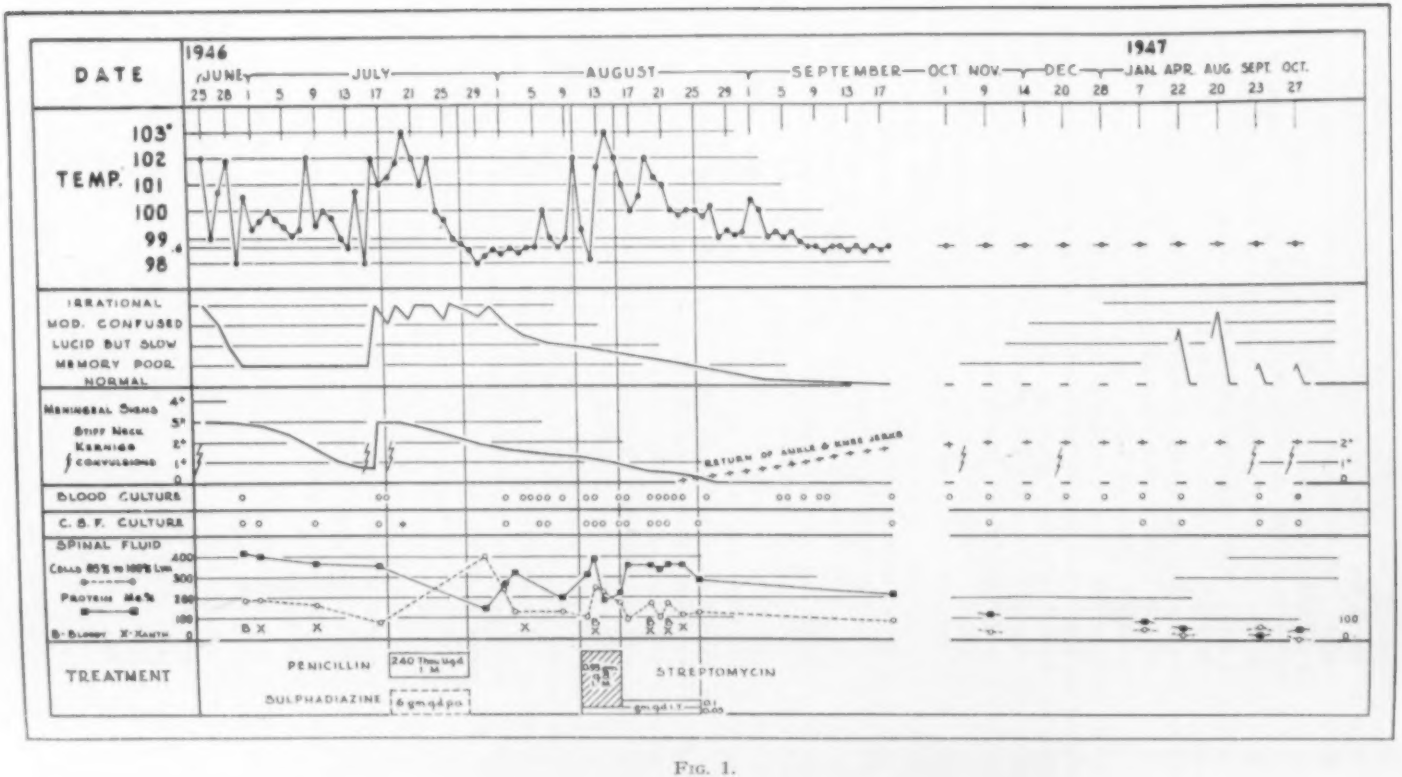
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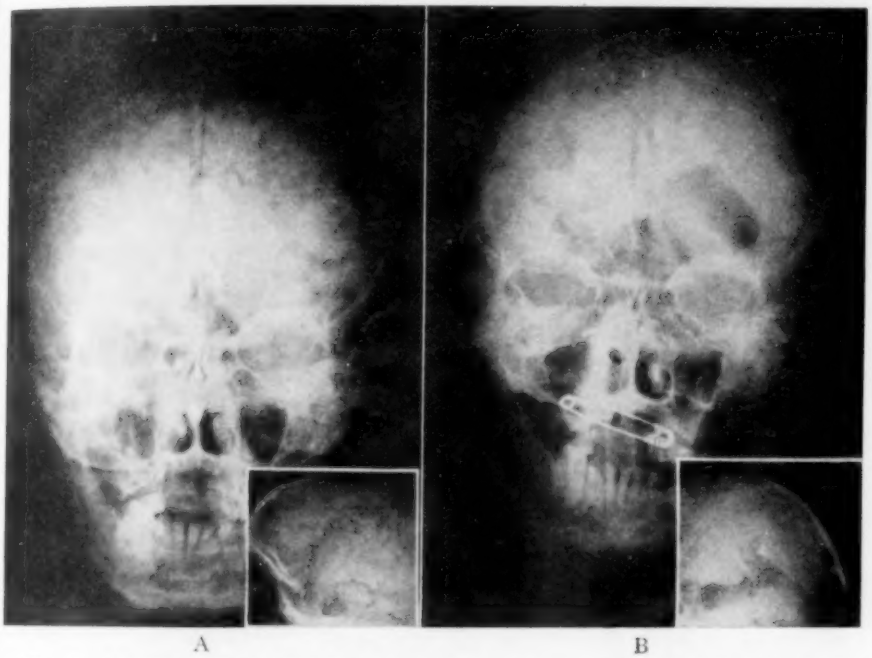
FIG. 1.

was no evidence of gross injury. Two hours later he was observed to have a brief, Jacksonian-type seizure, beginning in the left hand and spreading to the left face before becoming generalized. Following this, he lay quietly in bed staring at the ceiling, unresponsive to questioning or command. This course of events raised the possibility of a localization of the infectious process, either in the form of an abscess or granuloma, superimposed on what was then suspected to be a chronic meningo-encephaloradiculitis complicating chronic brucellosis. Arrangements were made for transfer to the Hartford Hospital, where appropriate neurosurgical investigation could be obtained more conveniently.

In a confused and semicomatose state he was admitted to the Hartford Hospital on the afternoon of July 17. In addition to the profound disturbance of consciousness,



A B

FIG. 2. Antero-posterior views obtained during (A) pneumoencephalography and (B) ventriculography in the patient H. P. In the former, slight increase in the size of the subarachnoid pathways is noted. This was present over the anterior two thirds of the brain in the lateral view (insert). In the latter (B) the ventricles appeared to be slightly dilated and their angles somewhat blunted.

signs of meningeal irritation had returned in force, with marked nuchal rigidity and strongly positive Kernig's. He had developed a variable tremor on the left arm and hand, with repetitive grasping movements of the latter. His head and eyes were generally turned to the right but not fixed in that position.

Throughout the 10-day stay at the Hartford Hospital his general physical examination, except for the neurologic findings, was remarkable only in a variable degree of fever and a blood pressure which varied from 130 to 180 mm. of mercury systolic over 80 to 120 diastolic. Except for occasional periods of relative rationality, when he was able to obey simple commands, he remained confused and at times was semicomatose and difficult to rouse. Transient visual and auditory hallucinations were frequent and, on occasion, lasted for several hours. He was incontinent of

both urine and feces, and the stools, which were frequent and loose and contained much mucus, were negative for blood, parasites and pathogenic bacteria. He had to be restrained in bed most of the time. There was no appreciable decrease in the signs of meningeal irritation. The deep tendon reflexes of the lower extremities remained absent, while those in the arms continued normally active.

The entire amount of cerebrospinal fluid, approximately 100 c.c., withdrawn on July 19 during pneumoencephalographic studies, was taken to the laboratory of the Connecticut State Health Department for culture for Brucella. On July 23 a right parietal burr hole was placed over the upper end of the motor strip (stimulation at this point produced movement of the contralateral great toe), and bilateral occipital burr holes were made for ventriculography. The pneumoencephalogram and ventriculogram are illustrated in figure 2. The dura visualized at all three points was "moderately thickened." A section of the biopsy of the cortex, described as "whiter and softer than usual," is illustrated in figure 3.

The routine laboratory studies during this 10-day period remained within normal limits, except for a fall in the hematocrit from 40 mm. to 34 mm. and, on one occasion, an elevation in the white blood count to 14,000 with 88 per cent polymorphonuclear leukocytes. The patient was given 6 gm. of sulfadiazine orally daily, and 240,000 units of penicillin intramuscularly in divided doses every three hours. Blood levels of free sulfadiazine ranged between 5.5 and 7.0 mg. per cent.

On July 26 he was returned to the McCook Memorial Hospital. He was confused, restless and disoriented, and restraints were still necessary. Penicillin and sulfadiazine were both discontinued at the time of transfer. For five days his mental state remained unchanged, with frequent episodes of visual and auditory hallucinations, followed by gradual but progressive improvement. Again meningeal signs subsided more slowly. His temperature fell to normal on July 28 and remained so until August 4. Small areas of anesthesia were noted over the palmar surface of the first phalanx of the left thumb and index finger. He complained frequently of severe generalized headaches, which were relieved by moderate doses of aspirin and codeine. In addition to weakness, he developed inconstant pain in both lower extremities, unrelated to activity. There was bilateral calf tenderness on both lateral and anteroposterior pressure, as well as bilateral positive Homans' signs, but no redness, swelling or increase in temperature. Tenderness was also acute along the sheaths of the dorsiflexors of the feet and the Achilles tendons, more marked on the right than on the left. There was, however, no definite evidence of deep or superficial phlebitis. This pain and tenderness of undetermined origin, suggestive of an extensive low-grade tenosynovitis but possibly "neuritic" in origin, was an inconstant and less frequent complaint throughout the remainder of his hospital stay.

On August 5, in spite of continued objective and subjective improvement, he again started to run an irregular fever. On this day the Laboratory of the Connecticut State Department of Health reported the cerebrospinal fluid culture of July 19 positive for a gram-negative rod, later identified as *B. abortus*.[4] In sensitivity studies of this organism, using tryptase broth as diluent and medium, growth occurred at a streptomycin concentration of 0.5 of a microgram per milliliter only after four days. Using the patient's spinal fluid as diluent and medium, no growth occurred with this same concentration of streptomycin. Treatment with streptomycin was started on August 10. For the next five days the patient received doses of 1,000,000 units daily; 50,000 units were given intrathecally daily, and the remainder in divided doses intramuscularly every three hours. On August 15 the intramuscular route was discontinued, and for the next 10 days the patient received 100,000 units of streptomycin intrathecally daily.

There was a marked difference between this second febrile period, which began before streptomycin was started and persisted after the drug was discontinued, and

the previous episode of July. While the one in July had been accompanied by a marked exacerbation of all the signs and symptoms, that in August was characterized by an increased sense of well-being and progressive improvement in signs. The variable but persistently abnormal cerebrospinal fluid findings throughout August are noted in figure 1. Spinal fluid pressures and dynamics which were examined on

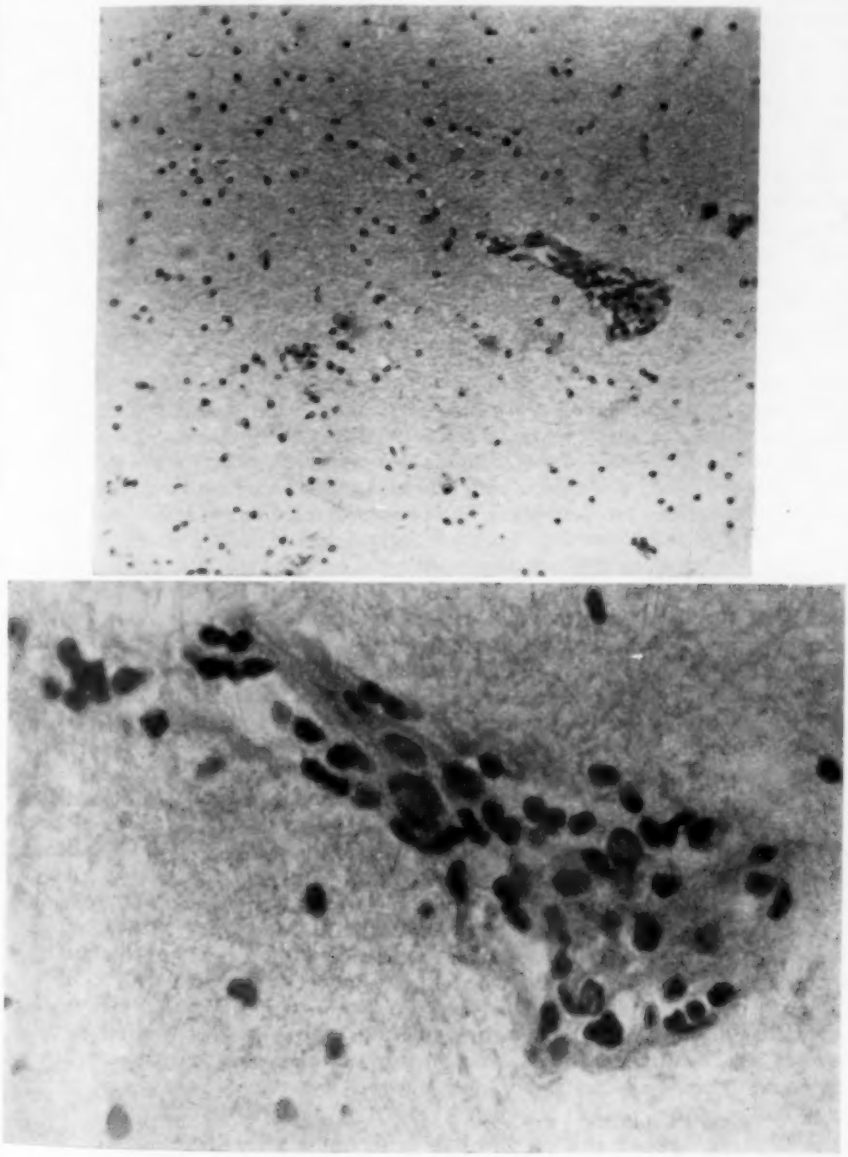


FIG. 3. Low and high power magnification of a section of the biopsy, taken from the upper part of the motor strip on the right showing perivascular round cell infiltration.

every tap, were all within accepted normal limits (120 to 160 mm. of C.S.F.). The remainder of the hospital course was marked by steady improvement. The deep tendon reflexes of the lower extremities were first observed to return on August 28, beginning with the ankle jerks; two days later slight knee jerks were obtained with reinforcement. From then on these reflexes grew progressively reactive, and all were considered normal at the time of discharge. With these changes came an associated gain in strength in the legs, with apparently more rapid recovery of the flexor than the extensor groups. His auditory acuity improved, both subjectively and to gross testing.

At the time of discharge on September 19, the neurologic examination was negative except for the following: Cerebration seemed normal but slightly retarded. Repeated subtractions were accomplished accurately but slowly. Amnesia was still present for events immediately preceding his illness and for the period spent in the Hartford Hospital, as well as for the first four days of his re-admission to the McCook Memorial Hospital. The small patches of anesthesia on the palmar surface of the first phalanx of the left thumb and left index finger remained. There was slight residual weakness of the extensor muscles of the legs, more so in the thighs and more marked on the right. Except for an increase of eight pounds in weight, his general physical examination remained as before. His hematocrit had risen to 42 mm. and the hemoglobin content to 90 per cent (Sahli).

Out of the 24 examinations of this patient's spinal fluid during July, August and September, gross blood was present on four occasions and xanthochromia noted on three others. Varying amounts of microscopic blood were present at all times during the period of hospitalization, ranging from 7 to 3,500 red blood cells per cu. mm. On four occasions the red blood cell count was over 2,000. During the latter part of August the red blood cell count, with one exception, was less than 25 cells per cu. mm. Agglutinations for Brucella in the patient's serum, tested on 23 occasions during this same period, showed a significant and persistent titer ranging from 1/320 to 1/640. A decrease in the intensity of the flocculation at these levels was noted, beginning in the latter part of August, but was followed by return to a 4 plus agglutination in a dilution of 1/640 in December. A total of 13 blood cultures and 23 clot cultures were all negative. On three occasions, cerebral spinal fluid agglutinations were positive in a dilution of 1/320. Twelve determinations of the opsonocytophagic index showed no consistent trend. The brucellergin skin test, using material which had produced positive reaction in two other patients, was negative on two occasions, one in the latter part of July and one in the middle of September.

Following discharge from the hospital on September 19, 1946, he returned to his tenement apartment for further convalescence. He continued to improve steadily. Dizzy spells were rare. Afternoon headaches, lasting three to four hours and relieved by lying down but not by aspirin, occurred with decreasing frequency. Pains along the lateral aspects of both legs and over the Achilles tendons and heels, lasting two to four hours and not associated specifically with activity, occurred from time to time. He had two convulsive seizures, one in the latter part of October and one on December 20. These were of short duration and not associated with incontinence, but were followed by headache and somnolence. In January, 1947, the patient reported that he felt better than at any time during the last two years. Subjective weakness and all awareness of fatigability on moderate activity had disappeared. The neurologic examination was negative save for the small area of anesthesia over the palmar aspect of the left thumb and index finger. The routine physical examination, including a complete blood count, urinalysis and sedimentation rate, was within normal limits. He had gained an additional 10 pounds. At this point he returned to work. A short time later, because of serious domestic difficulties which had

developed largely as a result of prolonged hospitalization, he left home and took a room by himself. This step was taken with the greatest reluctance, and he began to attempt periodically to drown his melancholy and loneliness in alcohol. From April to October, 1947, he was admitted to the McCook Memorial Hospital on four occasions for acute alcoholism (figure 1). On the first two he was confused, disoriented and suffering from auditory but no visual hallucinations. The last two admissions followed convulsive seizures. The clinical picture on no occasion suggested delirium tremens. Examinations of the cerebrospinal fluid during three of these four admissions revealed no abnormalities (figure 1). Because of the frequent hospitalizations and the irremediable nature of the environmental situation, it was thought advisable to transfer the patient to the Norwich State Hospital for a prolonged period of convalescence. He remained asymptomatic throughout his six months' stay in that institution, and was discharged in April, 1948. He returned to work in Hartford, continued to live alone and remained asymptomatic until August, 1948, when he had a convulsive seizure following another episode of acute alcoholism and again was admitted to the McCook Memorial Hospital. His general physical examination and neurologic examination were negative at this time. The routine laboratory studies were not remarkable and the cerebrospinal fluid findings were all within normal limits. After five days he returned to work and continued to be free of symptoms throughout the subsequent six months, with the exception of several episodes of considerable interest.

One afternoon in the latter part of September, 1948, he had the first of a series of sensory seizures. It began with a rapidly intensifying "ringing" in the left ear, followed abruptly by a "prickling" sensation over the left side of his scalp and rapid spread of this uncomfortable, almost "painful" sensation down over the entire left side of his body. The attack lasted about 20 minutes.

Once, early in December of the same year, and on two occasions in January, 1949, he had seizures of a different type, initiated by a sense of profound nausea accompanied by vomiting, followed abruptly by slight upward motion and partial flexion of both arms at the elbows. Coincidently, a "prickly" sensation developed around the scalp line, followed by convulsive movements of all extremities but no loss of consciousness except on one occasion.

On March 16, 1949, he had three sensory seizures within a period of four hours. These resembled the initial sensory attack in September, 1948, beginning with ringing in the left ear, followed immediately by painful paresthesias over the left side of the scalp, spreading down to involve the entire left side of body, and lasting about 20 minutes. The following morning he had four more similar seizures. One developed while an electroencephalogram was being taken* and another during a lumbar puncture. In the latter instance, when relaxation was obtained the initial pressure was found to be 180 mm. of cerebrospinal fluid. Ten cubic centimeters of clear fluid were obtained which contained only 3 red blood cells per cu. mm. and 32 mg. per cent concentration of protein. The Pandy test and agglutinations for Brucella were both negative. Agglutinations on the blood serum were positive for Brucella but only to a dilution of 1/80. The patient was started on dilantin and will be followed.

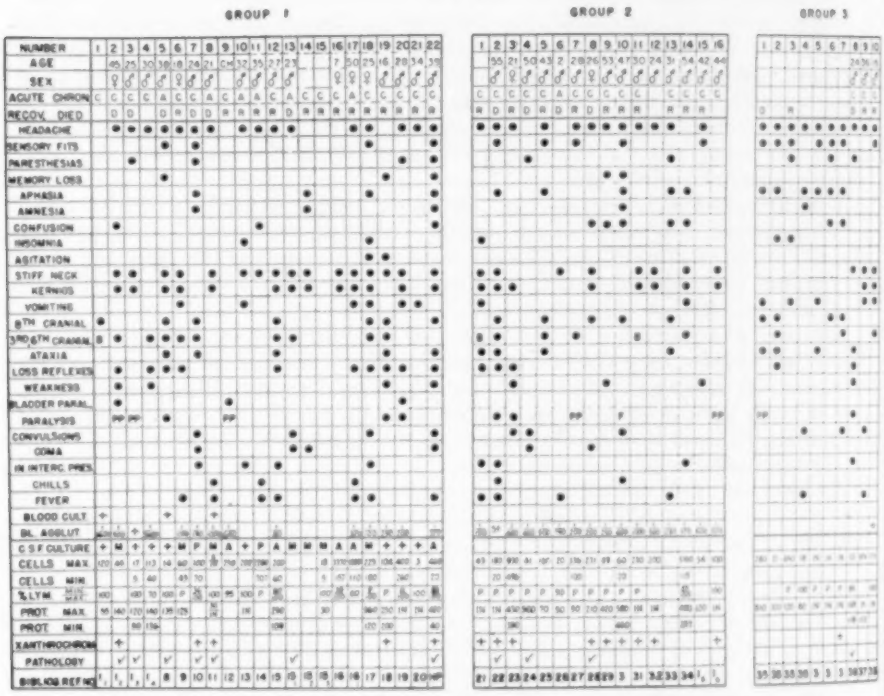
Comment

The recovery of the organism from the spinal fluid in this case was fortunate. The various serologic and bacteriologic tests employed did not

*This interesting electroencephalographic tracing, which will be reported in detail later by Dr. Wladimir T. Liberson and the author, indicated a superficial, well-outlined lesion in the right temporal lobe (spikes and sharp waves) and more extensive abnormality over the entire right hemisphere (slow waves).

suggest the presence of any other disease which might have confused or modified the course of this patient's illness. The history of a convulsive seizure in childhood and the attacks of headache resembling migraine suggest that the manifestations of cerebral dysfunction resulting from the infection may be modified in part by superimposition on a basically unstable cortex with a low convulsive threshold. The source of the original infection, the date of onset of specific symptoms and the effect on the course of this patient's disease of such modifying factors as periodic alcoholism and the various diagnostic and therapeutic procedures employed appear to be

TABLE I



The majority of the symbols are self-explanatory; for acute (A), chronic (C), recovered (R) and died (D). In case 9, CH stands for child. Signs and changes related to visual function are all included in the heading (3rd, 6th Cranial). The 3rd nerve was most often involved, occasionally the 6th and rarely both. Blindness (B) was noted to be accompanied in one instance by optic atrophy. Paralysis was limited to one extremity, except in one instance in which the facial (F) nerve was involved, and in those cases where paralysis of both legs resulted in paraplegia (PP). A (+) sign indicates a "positive" agglutination, titer not noted; a positive culture for Brucella, strain not specified; and the presence of xanthochromia, in their respective headings. The maximum and minimum cell count, protein content, and lymphocyte percentage is noted in those cases in which more than one determination of these aspects of the final fluid was made. A (V) mark indicates that some description of the pathology, gross, microscopic or both, is available in the specific case. In reference to laboratory data (St) stands for strong, (IN) increased, (P) predominantly.

matters of pure speculation. The daily intrathecal administration of 0.05 of 0.1 gm. of streptomycin may have contributed to the variability and intensity of the spinal fluid abnormalities during the period it was used.[50] The prolonged course of this illness, with its striking exacerbations and remissions, the evidence of meningeal and encephalitic involvement and the relative absence of localizing neurologic signs, presented the most striking clinical features. It would not seem that any conclusions could be drawn regarding the effect of specific treatment in this case.

The material included in table 1 represents a tabulation of certain clinical and laboratory findings on a group of proved or suspected cases of central nervous system brucellosis selected from the foreign and domestic literature available for personal review by the author. Consideration was limited to those cases in which the central nervous system involvement appeared to represent dissemination of the disease process in a general sense. Instances in which invasion of the central nervous system presumably resulted from extension of a local lesion, as may occur from an osteomyelitic lesion in vertebra [5, 39] or skull,[6] or as a metastatic infection during the course of an endocarditis,[7] were not included. No attempt was made to review the voluminous literature dealing with the purely psychiatric complications attributed to chronic brucellosis.

Only reported positive findings have been included in this table. With rare exceptions, the case reports were brief and lacking in detail. In certain cases neither the age nor the sex of the patient was mentioned.

Group I consists of 22 cases, including the one reported in detail in this paper, in which invasion of the central nervous system by Brucella was established by recovery of the organism from the cerebrospinal fluid or by direct culture from infected central nervous system tissue at the time of operative exploration.

Group II includes 16 cases in which cerebrospinal fluid abnormalities, accompanied by specific agglutinations for Brucella in high titer, in all but three cases in a dilution of over 1/200, strongly suggested invasion of the central nervous system by this organism. In case 13 of this group, a British physician, no examination of the spinal fluid was made. The case was included in this group, however, because of the very high agglutination titer (1:1,280), and certain "pathognomonic" aspects of the clinical picture.

Group III is made up of 10 cases in which the signs and symptoms of a meningo-encephalitis, accompanied by increased cells and protein in the cerebrospinal fluid, following in each instance, by a period of months, a "characteristic" acute attack of undulant fever, suggested the diagnosis of central nervous system brucellosis.

In all cases in the three groups the possibility of syphilis, or complicating tuberculous meningitis in the fatal cases, appeared to be satisfactorily ruled out.

Discussion of Table I

Age. The age of the patients ranged from two to 55 years. In 11 instances the patient's age was not noted. Of the remaining, the majority fell in the third and fourth decades, with the rest scattered through childhood and the second and fifth decades.

Sex. The sex incidence was predominantly male. It was not noted in 12 cases.

Duration of Illness. For simplicity, data referring to the duration of illness were omitted from the chart, but they seem best inserted into the discussion at this point. The incidence of a previous illness suggesting acute brucellosis, the duration of symptomatology of a nonspecific nature leading up to the onset of definite neurologic symptoms, and the subsequent duration of the illness were in many instances difficult to determine. Specific attacks of acute brucellosis followed by remissions before the onset of neurologic complication were noted in seven cases in Group I, eight cases in Group II and all the cases in Group III. The interval between the initial acute attack of brucellosis and the onset of symptoms leading up to specific signs of central nervous system involvement ranged from two months to two years. In the great majority of cases this interval was less than a year's duration. The duration of nonspecific symptoms preceding the onset of neurologic symptoms was noted in eight cases in Group I, and ranged from four weeks to six months, and in 10 cases in Group II, from two weeks to a year, the majority lasting from four weeks to four months. This period could not be determined in Group III. Three months was selected arbitrarily as the dividing line between the acute and chronic cases. There were five cases in Group I with a duration of less than three months, one in Group II and none in Group III. The remaining chronic cases extended over a three-month to two-year period, with the great majority lasting approximately four to six months.

Mortality. There were six deaths in Group I, two of which occurred before three months; four in Group II, one occurring before three months, and two in Group III, the duration of illness not known. In two cases in Groups I and II, respectively, and five cases in Group III, the outcome could not be determined. The absence of specific data regarding prolonged follow-up made it impossible to determine the incidence of possible subsequent recurrences in "recovered" cases.

Symptomatology and Signs. The value of the data on symptomatology in this table is limited by the fact that the majority of cases were not reported in detail. Apparently only what were considered the most important positive clinical signs were noted in the original reports. An attempt to list complete negative findings was universally absent. In almost every instance, blank squares represent a lack of evidence rather than a negative finding.

Headache was the most common symptom. Details as to the type, severity and localization of the pain were mentioned in only a rare instance.

They were described as transient, episodic, and subject to remissions and exacerbations. The presence of headaches was not noted in 10 cases.

Paresthesias and Sensory Fits. These sensory phenomena have been arbitrarily divided into separate headings in table 1. *Sensory fits* applies specifically to attacks of hemiparesthesia. *Paresthesias* include sensory disturbances limited to one extremity or a portion of one extremity, most often an arm and rarely bilaterally. They were described in all but two cases in Group III, in one-half the cases in Group II, and in one-quarter of the cases in Group I. Their occurrence was episodic, lasting for a matter of minutes up to one to two hours, and apparently represented a most dramatic phenomenon, with great variation in frequency of recurrence.

Memory Loss and Amnesia. Disturbances of memory and periods of amnesia were noted in approximately one-fifth of the cases. This disturbance was also episodic and variable in duration.

Aphasia. Transient episodes of speech disturbances, lasting from minutes to hours, described in the majority of instances as aphasia and in a few as dysarthria, were noted in approximately one-third of the cases.

Confusion. Periods of confusion and disorientation of varying severity, lasting from hours to a few days, occurred periodically in approximately one-quarter of the patients.

Sleep Disturbance. Insomnia or somnolence was noted in five cases.

Agitation. Transient periods of agitation were described in two cases.

Meningeal Irritation. Nuchal rigidity and/or positive Kernig's signs and/or vomiting were noted in the great majority of cases. These as well as other objective signs of central nervous system involvement were apparently a much less dramatic aspect of the picture than the periodic symptomatology.

Cranial Nerve Involvement. Involvement of one or more of the first, third, sixth or eighth cranial nerves was noted in over one-half the cases. Of these, the eighth was most frequently affected.

Ataxia. Ataxia was noted in approximately one-quarter of the cases. In most instances it was not possible to determine from the data whether this was due to general weakness, loss of motor power of specific muscles, or loss of position sense.

Reflex Changes. Reflex changes were noted in approximately one-third of the cases. In a great majority these represented loss or marked diminution of the deep reflexes in the legs. Hyperactive reflexes in the lower extremities were described in three instances. A positive Babinski sign was reported in only two cases.

Weakness of Legs. Specific weakness of the leg muscles was described in eight instances. In six cases it was associated with diminished or absent deep reflexes.

Bladder Paralysis. Urinary retention was described in only three cases, in one instance associated with hemiparesis, and in two with paraplegia.

Paresis. Paralysis was observed at one time or another in 13 cases, including six paraplegias, one case of facial paralysis, two of hemiparesis, two of paralysis of one arm, one of transient episodic hemiparesis and one not specified.

Convulsions. Convulsions were noted in approximately one-fourth of the cases. In two instances these were described as Jacksonian in nature, and in one other the seizures were associated with choreiform movements.

Sensory Findings. Objective sensory abnormalities were not described in any instance.

Coma. Comatose states were noted in five cases, in two instances as terminal phenomena.

Chills and Fever. Chills were specifically mentioned in four cases and fever in 12, or approximately one-fourth of the cases.

Laboratory Data:

Blood Culture. A positive blood culture was mentioned in only three instances.

Agglutinations. Positive agglutinations for Brucella were noted in 29, or one-half the cases, and not recorded in the remaining. In two instances it was simply described as "positive" and in another as "strong." Except for one agglutination of 1:80, one of 1:100 and one of 1:150 the dilution titers ranged from 1:200 up to 1:5,000.

Cerebrospinal Fluid Culture. A Brucella organism was cultured from the cerebrospinal fluid or directly from a central nervous system lesion in 22, or approximately one-half the cases.

Cerebrospinal Fluid Findings:

Cells. The maximum number of cells reported in individual cases ranged from three to 5,700, and the minimum number of cells from five to 707. In one instance an increase in cells was noted, amount not specified. In one case no increase in cells was reported. As far as could be determined, these counts did not include red blood cells. Gross as well as microscopic blood was noted at varying times in a number of cases.

Lymphocyte Percentage. In general, lymphocytes were the predominating cells present. In one instance they ranged from 0 per cent in an initial examination to 100 per cent in another. In other cases a wide variation within this range was noted.

Protein Concentration. Protein concentration ranged from 13 mg. per cent to 810 mg. per cent in 25 cases in which it was numerically reported; in 11 cases it was reported as increased, and in eight it was not mentioned. In each instance in which more than one determination was made there was a wide range in concentration on various determinations.

Xanthochromia. Xanthochromia was noted in 17, or approximately one-third of the cases. In certain instances in which multiple taps were made, it was present as a variable and recurrent finding.

Pathology. Pathologic reports of variable completeness were described in 12 cases.

In the more general discussions of this disease,[1, 2, 3, 15, 38] a number of features have been considered of particular significance. Attention has been called to the fact that this complication may arise at any time during the acute or chronic phase of brucellosis and even following prolonged remissions. Transient brief episodes of hemiparesthesias and paresthesias have been considered a "pathognomonic" feature of the disease, hypothetically explained on the basis of spasm of the Sylvian artery. In this regard, analogies have been suggested with similar symptoms occasionally occurring in meningovascular syphilis in which the inflammatory lesion is also primarily vascular in nature. The most characteristic feature of the symptomatology in meningo-encephalitis due to brucellosis appears to depend not so much on the nature of the symptoms themselves as on the dramatic episodic manner of their occurrence over prolonged periods. Much emphasis has been placed on the extent and predominance of meningeal involvement in the great majority of cases and the frequency of disturbances in cranial nerve functions, particularly the eighth, presumably secondary to chronic basilar meningitis. Other features of importance are the relative absence of localizing neurologic signs and the presence of a low-grade, variable fever. Most of these observations are generally supported by the limited data in table 1, as well as by the general description of the spinal fluid findings of predominant lymphocytosis, extreme variability in the number of cells and the protein content, and the not infrequent occurrence of xanthochromia or other evidence of minor subarachnoid bleeding.

Pathology

The general aspects of the pathology of brucellosis have recently been reviewed.[40] Material obtained from experimentally infected animals and from cases of human brucellosis shows a predilection of the organism for tissues belonging to the reticuloendothelial system, a strong tendency to intracellular parasitism of nonphagocytic cells,[30] and to the formation of nodular granulomatous lesions. The latter have been noted in many instances to be indistinguishable from the nodular lesions of Boeck's sarcoid and noncaseating tuberculosis,[40, 41] Hodgkin's disease [42] and lymphogranuloma venereum.[41] The effect of tissue immunity or hypersensitivity on the course of the pathologic process in brucellosis is not known. It is well recognized that the pathogenicity of the various strains of Brucella is different for a variety of animals and for man, and distinct differences in the pathologic lesions produced by different strains of Brucella in the same animal have been observed.[44] Necrosis is a rare occurrence, though the organism has been cultured from the blood in cases of endocarditis,[6, 7] from osteomyelitic lesions of the skull,[6] from a pericholecystic abscess [40] and from

pleural and empyema fluid.[43] In experimental infections in chick embryos the parasite has shown a predilection for vascular endothelium.[49] The following pathologic changes in the central nervous system have been attributed to Brucella.[1c, 1d, 8, 10, 11, 15b, 22, 24, 28, 36]

1. Various degrees of vascular inflammation, from minimal perivascular infiltration with lymphocytes, plasma cells and macrophages to acute inflammation of the vessel wall with polymorphonuclear infiltration, adventitial thickening with connective tissue, necrosis and aneurysmal formation. In one instance, death followed rupture of a mycotic aneurysm of the basilar artery.[10]

2. Diffuse meningeal involvement by the same type of inflammatory process with thickening and congestion of the meninges, acute and chronic inflammatory cell infiltration, and connective tissue proliferation. In one instance, obstruction of the foramina of Luschka and Monro by this process had produced an internal hydrocephalus.[1d] Hemorrhagic pachymeningitis was reported in one case.[24]

3. Diffuse granulomatous cellular infiltration of the meninges, with nodular formation varying from small tubercle-like masses of hyalinized connective tissue moderately infiltrated with chronic inflammatory cells to larger nodules containing areas of central necrosis and polymorphonuclear infiltration.

4. Inflammatory cell infiltration into the perineurium of nerve roots, with hydropic changes in the central portion of the nerve and condensation of the nerve fibers peripherally.

5. Edema of the cortex, with lymphocytic infiltration and fatty pigment deposition in the perivascular sheaths; inflammatory reaction in the ependyma and subependymal tissues, perivascular round cell infiltration and granuloma-like cellular infiltration in the cortex, and encephalomalacia. In one case, *B. abortus* was recovered from the contents of a brain cyst.[20]

In general, the extensive and advanced inflammatory reaction in the meninges contrasted markedly with the relatively limited and less intense involvements of cortical and subcortical tissues. In certain instances, the inflammatory reaction was limited to the meninges alone.[8, 17]

Bacteriology

Attempts to recover Brucella from infected material must take into consideration certain fundamental differences in the cultural requirements of the various strains of the organism.[44] *Brucella abortus,* by far the most common variant responsible for human brucellosis in New England, was cultured from the cerebrospinal fluid of our patient in the laboratory of the Connecticut State Department of Health.[4] The infrequent recovery of this organism from the spinal fluid, even when the most carefully considered methods are employed, suggests that the organisms are present at any one time usually in only small numbers and under circumstances that may be

largely fortuitous, conditions which might be expected in the light of the tendency of Brucella to intracellular parasitism. In the case reported here, an inoculum of approximately 80 c.c. of spinal fluid was cultured. The chances of recovery appear to be increased by the use of a large inoculum (10 c.c. or more),[12] and by the inoculation of both cultures [10, 17] and guinea pigs [10] with the centrifugal sediment of large quantities of spinal fluid. In one case an attempt was made to enhance the effect of centrifugalization by the prior addition of heat-inactivated, polyvalent anti-Brucella rabbit serum.[16] The organism has been recovered from the guinea pig in instances when other cultural methods have failed.[9] Significant titers of Brucella agglutinins have been demonstrated in the spinal fluid in several instances.[27, 28, 9]

Diagnosis

The diagnosis of central nervous system brucellosis, a rare complication of an ill defined and highly variable infectious disease, will depend primarily on its consideration as a possible answer to otherwise unexplained cases of meningo-encephalo-myelo-radiculitis, particularly where the illness is prolonged and is accompanied by an intermittent low-grade fever. It is evident from the discussion and data included in table 1 that a number of findings related to the history, clinical course or laboratory investigation of any case might suggest the possibility of central nervous system brucellosis. It is most likely, however, that a case with no history of a previous acute attack of brucellosis would first suggest a variety of other possible explanations for immediate consideration, e.g., one of the more common forms of chronic and acute meningo-encephalitis with a tendency to lymphocytosis in the cerebrospinal fluid, particularly tuberculous meningitis, meningovascular syphilis, or lymphocytic choriomeningitis. Apparently the disease may simulate at any one time a great variety of central nervous system lesions in addition to those already mentioned, including "idiopathic" epilepsy, brain abscess or chronic "nonspecific" arachnoiditis. Suspicion or even proof of invasion of the central nervous system by Brucella would not appear to obviate the advisability of excluding by appropriate studies other more frequently encountered sources of central nervous system pathology which might act as complicating or modifying factors. Like psychoneurosis, the diagnosis of brucellosis carries with it the danger of affording a ready explanation for the most varied symptomatology, both present and future.

The diagnostic importance of recovering a Brucella organism from the spinal fluid or infected central nervous system tissue is apparent, and the advisability of high speed centrifugalization of as large amounts of spinal fluid as can be obtained for careful culture and guinea pig inoculation of the sediment in suspected cases has already been mentioned.

A positive blood or spinal fluid Brucella agglutination, especially one of high titer, is of great importance in creating a high level of suspicion regarding the diagnosis.

Tests to demonstrate skin sensitivity to Brucella antigens or determinations of the opsonocytophagic index would appear to be of no value in supporting or discouraging a diagnosis of clinically significant brucellosis in individual cases.

Treatment

Improvement or recovery in central nervous system brucellosis has accompanied the use of convalescent serum,[16, 16b] nonspecific typhoid vaccine,[23] specific vaccine therapy,[1] "toxic" filtrates [14] and streptomycin.[34] As 21, or approximately one-half the cases listed in table 1, were reported as improved or recovered without mention of specific treatment, any direct relationship between one or another of these different therapeutic approaches and the outcome of the disease would seem doubtful and certainly impossible to prove. For the present, treatment of this rare complication must reflect experience in the treatment of the more common forms of the disease. The natural course of brucellosis is characterized by a tendency to variable and unpredictable remissions and exacerbations, and apparently to recovery in the great majority of cases. Against such a shifting and uncertain background, the accurate delineation of the usefulness of any therapeutic agent is extremely difficult and, for the present, would appear to be impossible except over a long period of study. This problem is further complicated by the variable pathogenicity of the different strains of the parasite for both man and experimental animals, and the differences which might be expected in sensitivity of the various strains to a given therapeutic agent. Regarding some of the agents more recently employed, the value of combined sulfadiazine and streptomycin treatment [45] of acute and chronic brucellosis has not yet been determined and is not without danger.[46] The use of aureomycin in the treatment of acute brucellosis has met with both encouraging [48] and discouraging [47] results.

Summary

A case of chronic meningo-encephalo-radiculitis in which *Brucella abortus* was recovered from the cerebrospinal fluid has been described in some detail. The clinical features and laboratory findings associated with this manifestation of brucellosis have been reviewed. The pathology, bacteriology and treatment of this condition, as well as certain features related to the diagnosis, have been briefly discussed.

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CASE REPORTS

MILIARY TUBERCULOSIS IN A CORTISONE TREATED PATIENT: CASE REPORT WITH AUTOPSY *

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A case of acute miliary tuberculosis in a patient receiving cortisone for a chronic febrile illness with arthritic manifestations has recently been observed by us. We have not been able to find a similar instance reported in the literature, although active tuberculosis has been enhanced and aggravated by administration of cortisone to experimental animals.

Spain and Molomut [1] produced tuberculosis in guinea pigs and later treated them respectively with cortisone, with streptomycin, and with a combination of cortisone and streptomycin. Autopsy studies showed the lesions in those receiving cortisone to be more extensive, more widely distributed and less well localized than in the others. The authors suggest that cortisone has no place in the treatment of human tuberculosis, and that a flare-up of a previously unrecognized latent tuberculosis might occur as a result of its use in conditions such as rheumatoid arthritis. Hart and Rees [2] were able to produce a chronic type of tuberculosis in mice. Cortisone markedly exacerbated the chronic pulmonary infection, with a resulting high mortality. The more acute type of tuberculous infection was also enhanced by cortisone. The authors warn that tuberculosis in man may possibly be aggravated similarly.

McNee [3] states that wounds showed no sign of healing and abscesses no signs of granulation tissue formation in patients (or animals) to whom the hormone was being administered, and warns that the effect on the granulation tissue barrier around an active tuberculous lesion might be disastrous. He further states that he has heard of serious side effects, including acute spread of tuberculosis, but no details are furnished.

Thorn et al.,[4] in a review of the clinical usefulness of ACTH and cortisone, mention three patients with tuberculosis who were treated with ACTH. The first was a patient of Favour's who was given 100 mg. ACTH per day for 12 days for far advanced pulmonary tuberculosis. During treatment the temperature and pulse became normal, the sedimentation rate fell to zero, and the tuberculin test became negative. Sputum and thoracotomy drainage diminished and night sweats ceased. The appetite became ravenous and euphoria developed. A chest film showed no significant change. After discontinuance of ACTH there was an exacerbation of the disease. The other two patients, reported by Freeman et al.,[5] experienced similar clinical changes when ACTH was administered. In one, however, there was definite spread of the tuberculosis during the period

* Received for publication March 16, 1951.
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of administration. Tomsett et al.[6] noted striking benefit from the administration of ACTH to four patients with far advanced tuberculosis. Evidence of healing of the laryngeal lesions was observed, but the signs of acute illness returned when the drug was withdrawn.

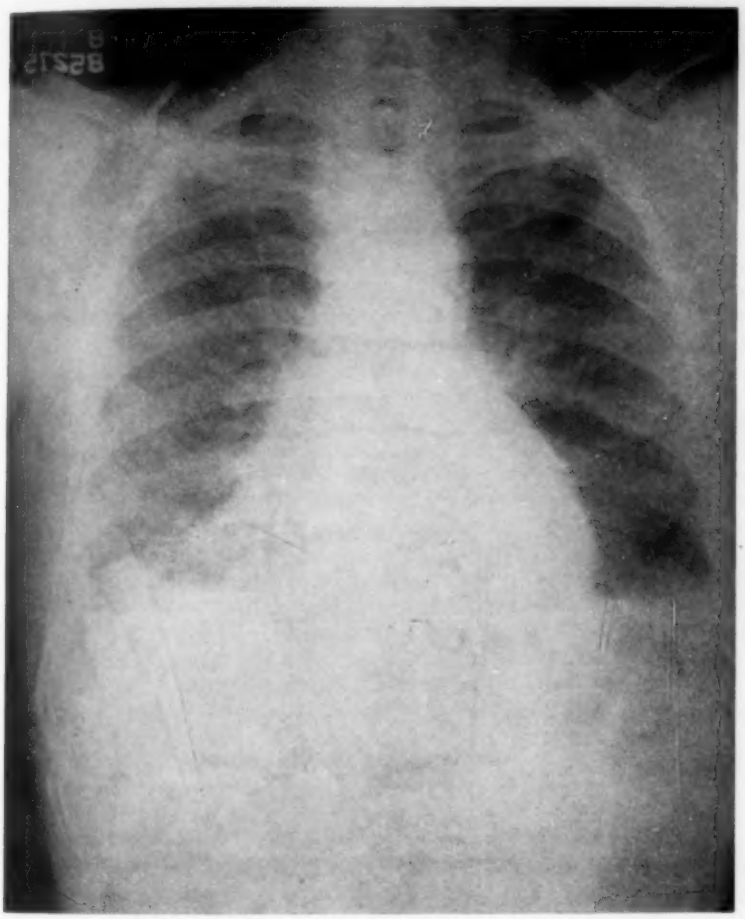

FIG. 1. Roentgenogram of the chest, showing increased density in both lower lung fields, more marked on the right. Miliary tubercles were not seen in any of seven films.

CASE REPORT

A 59 year old white butcher was admitted June 28, 1950, complaining of fever, joint pains and chest pain. Evening fever, ranging up to 103° F. and associated with chilly sensations, sweating and weakness, had been present for three weeks. Joint pains involving the hips, knees, shoulders and small joints of the hands had been experienced for three years. At times the involved joints were swollen. In 1943 the patient had had an attack of precordial pain, dyspnea and vertigo. Since then he had had chest pain on exertion, radiating to the left arm and relieved by nitroglycerin. In November, 1949, he had pneumonia; following this he continued to complain of bi-

lateral anterior chest pain, which was made worse by deep breathing. Appendectomy had been performed in 1926. The only pertinent fact in his family history was the death of both aged parents of heart disease.

Physical examination revealed a rather sallow, chronically ill white male. The temperature was 101.8° F.; pulse, 88; respirations, 26; blood pressure, 106/70 mm. Hg. Funduscopic examination showed grade 2 retinal arteriosclerosis, with several small, partially absorbed retinal exudates temporal to each optic disc. The ears, nose and throat were normal. No lymphadenopathy was found. Dullness, diminished breath sounds and sticky râles were present at both lung bases. The heart was not

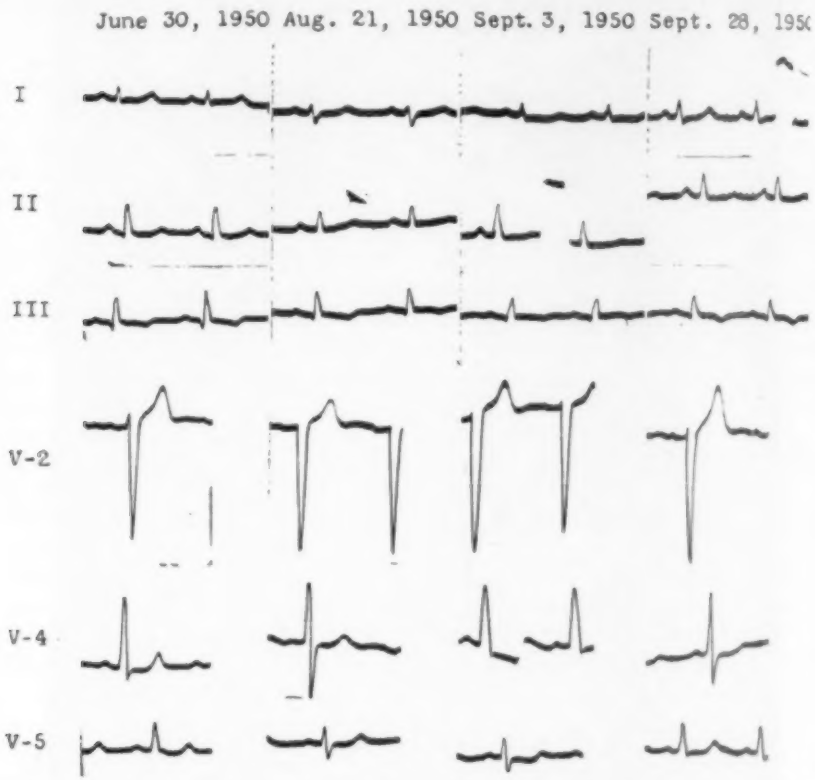

FIG. 2. Electrocardiograms, showing sinoauricular rhythm and low voltage in the limb leads. Changes in voltage and form of QRS complexes and T waves are encountered in serial tracings.

enlarged. The rhythm was regular. No murmurs were heard. The abdomen was normal except for the presence of a healed right rectus scar. The liver and spleen were not palpable. Slight periarticular thickening of both knee joints was noted, but no evidence of disease of the other joints was found. No arterial pulsations were palpable in either foot, although good femoral pulsations were present bilaterally.

Laboratory Tests: Red cell count, 4,500,000; hemoglobin, 11 gm. per 100 c.c.; white cell count, 7,800, with 88 per cent polymorphonuclear leukocytes, 8 per cent lymphocytes and 4 per cent eosinophils. Urinalyses were normal except for the presence of occasional red cells in the urinary sediment. Sedimentation rate was 40 mm.

in one hour. Multiple blood cultures showed no growth. Blood Wassermann and Kahn tests were negative. Serum agglutination for brucellosis was negative. Blood sugar was 76; urea nitrogen, 10.6 mg. per 100 c.c. Serum albumin was 1.94; globulin, 5.05 gm. per 100 c.c. Repeated sputum examinations for acid-fast bacilli, fungi and tumor cells were negative. Roentgenologic examination of the chest showed a pneumonitis of indeterminate origin in both lung bases, more marked on the right, with limited pleural effusions in both costophrenic angles (figure 1). Electrocardiograms showed low voltage of QRS complexes in the limb leads (figure 2).

The patient continued to have pain in the knees, ankles and shoulders, with little or no objective evidence of joint disease. The temperature ranged irregularly between 98.6 and 104° F. Salicylates, penicillin, aureomycin, chloramphenicol and streptomycin seemed to have little effect upon the course of the disease. A small nodule appeared about July 1 in the region of the right temporal artery. Biopsy showed hyalinized connective tissue with no evidence of a vascular lesion. A thoracentesis was performed and a few cubic centimeters of bloody fluid were removed from the right pleural space. The fluid was negative for tumor cells and sterile on culture. Slight edema of the lower extremities appeared. Nearly three months after the first nodule was discovered, another small nodule was noted over the right radial artery at the wrist. Biopsy showed only a mild chronic dermatitis and localized subcutaneous cellulitis. Both biopsy wounds were observed to heal rapidly while the patient was receiving cortisone. Several other nodules developed in various parts of the body, but these were not biopsied. Beginning July 8, a 30 day course of cortisone, 100 mg. intramuscularly daily, was given, with considerable relief of the joint pains but little change in the objective findings. Elevation of temperature continued, and the sedimentation rate remained rapid. The cough and chest pain were unchanged, as were the physical signs in the chest. The patient experienced a definite euphoria and his appetite improved. An increase in the preëxisting edema of the legs and a gain in body weight occurred, and these were controlled by the restriction of sodium and administration of ammonium chloride and a mercurial diuretic. A second course of cortisone (17 days) was given in August, and a third course (25 days) in September, with approximately the same effect noted initially. The patient died suddenly and unexpectedly on October 17, the one hundred twelfth hospital day.

Autopsy Findings: Slight emaciation was evident. Each pleural space contained 250 c.c. of clear, straw-colored fluid. The lungs were bound to the chest wall by fibrous adhesions. The heart was slightly enlarged.

Lungs: The left lung weighed 1,075 gm., the right 850 gm. They were firm and boggy, and on section they showed edema, congestion and granularity. Microscopic sections showed collapse, fibrosis and moderate anthracosis. Phagocytic cells containing old blood pigment were found. Organizing and organized pneumonic exudate was present in the air spaces in most of the sections. The most active process was a tuberculous inflammation, in which miliary and a few early conglomerate tubercles were found (figure 3). The only vascular lesion consisted of some hyaline thickening of the vessels. The sections of peribronchial lymph node showed typical and still active caseous and extensively conglomerate tuberculosis. A narrow margin of fibrosed lymph node was still present, and in this a few miliary and early submiliary tubercules were seen.

Heart: The heart weighed 375 gm. The left ventricular wall measured 2.5 cm. in thickness, the right 1 cm. The valves and chambers were normal. The coronary arteries showed marked thickening and calcification of their walls. The lumen of the anterior descending branch of the left coronary artery was pinpoint in caliber. No thrombus was demonstrated. The aorta showed marked intimal disease, with atheromatous ulceration and calcification. Microscopic section showed extensive fibrosis of the myocardium. The small branches of the coronary vessels showed no thickening.

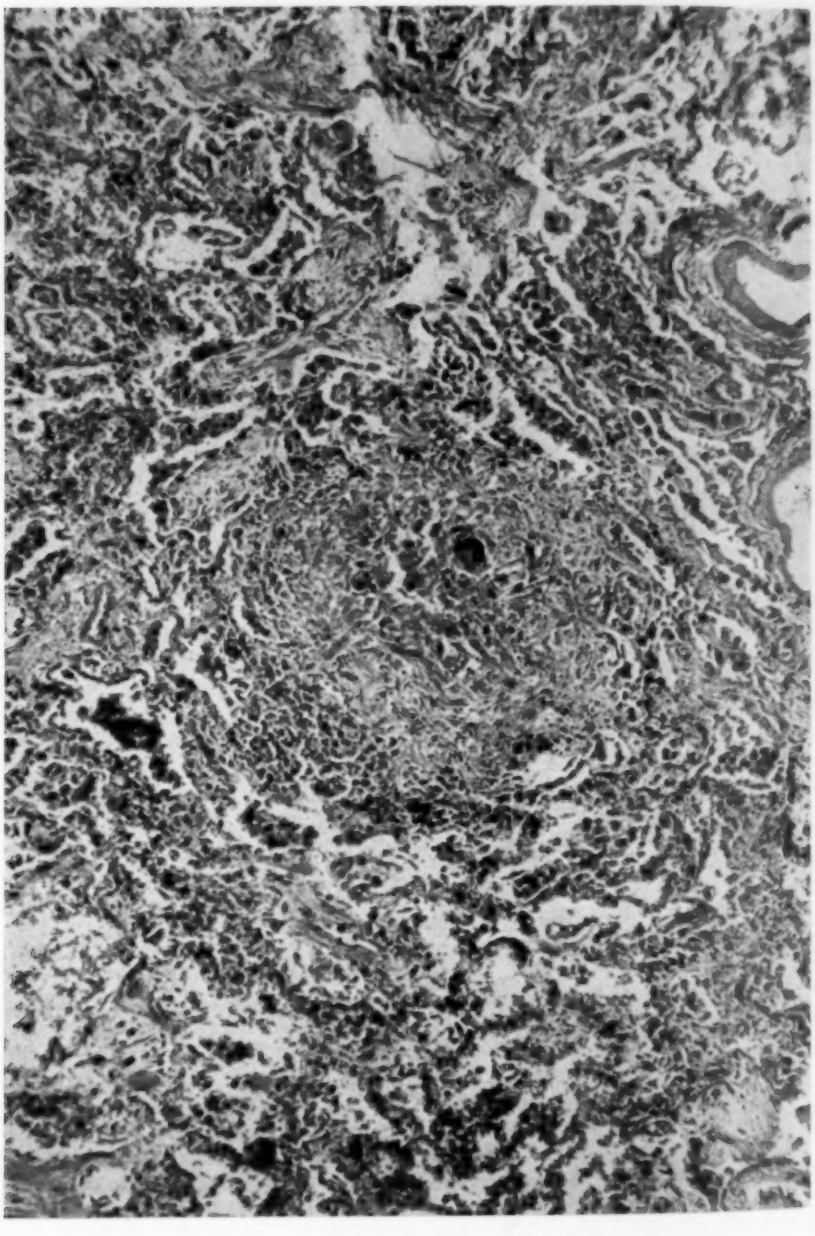

FIG. 3. Photomicrograph (× 120) of section of lung, showing an early conglomerate tubercle with a Langhans' giant cell. The surrounding lung shows inflammatory exudate in the alveoli and an increase in stroma. No vascular lesion is evident.

Fig. 3. Photomicrograph (× 120) of section of lung, showing an early conglomerate tubercle with a Langhans giant cell. The surrounding lung shows inflammatory exudate in the alveoli and an increase in stroma. No vascular lesion is evident.

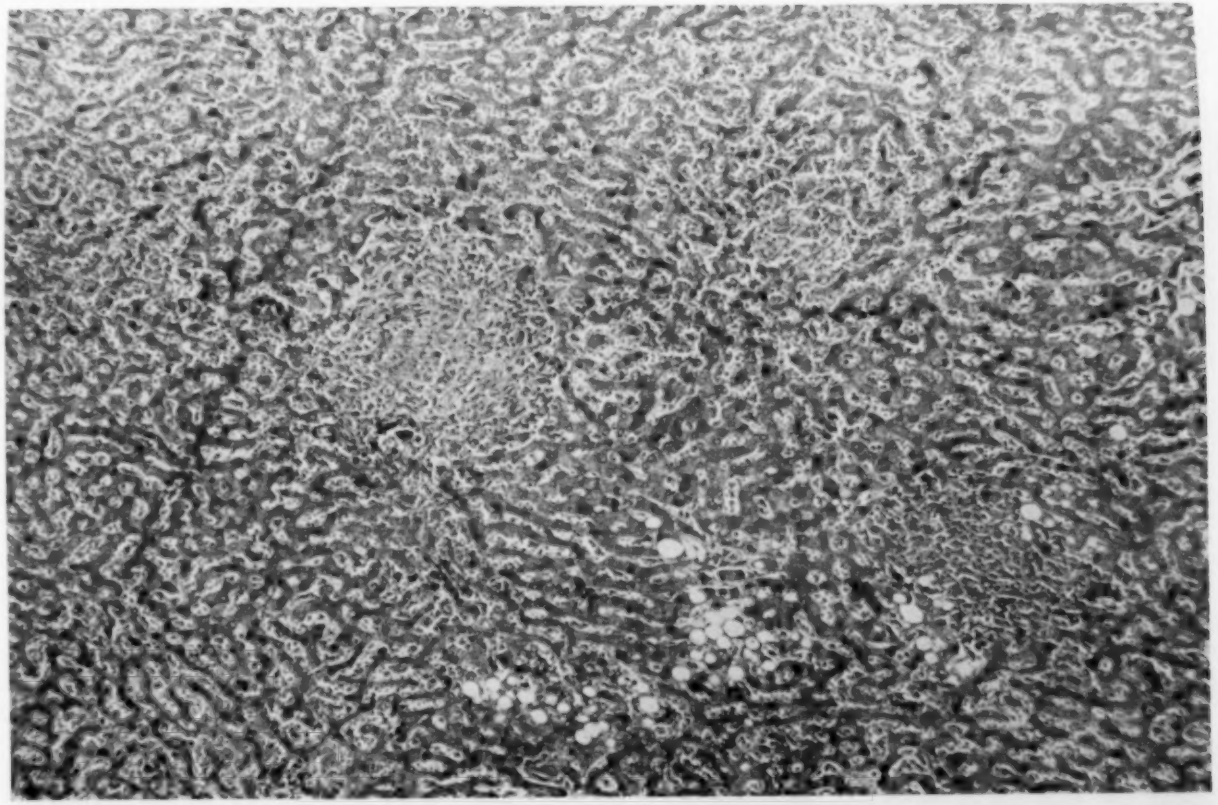

Fig. 4. Photomicrograph (× 120) of section of liver, showing typical miliary tubercles. The hepatic cells show granular degeneration. The sinusoids are engorged.

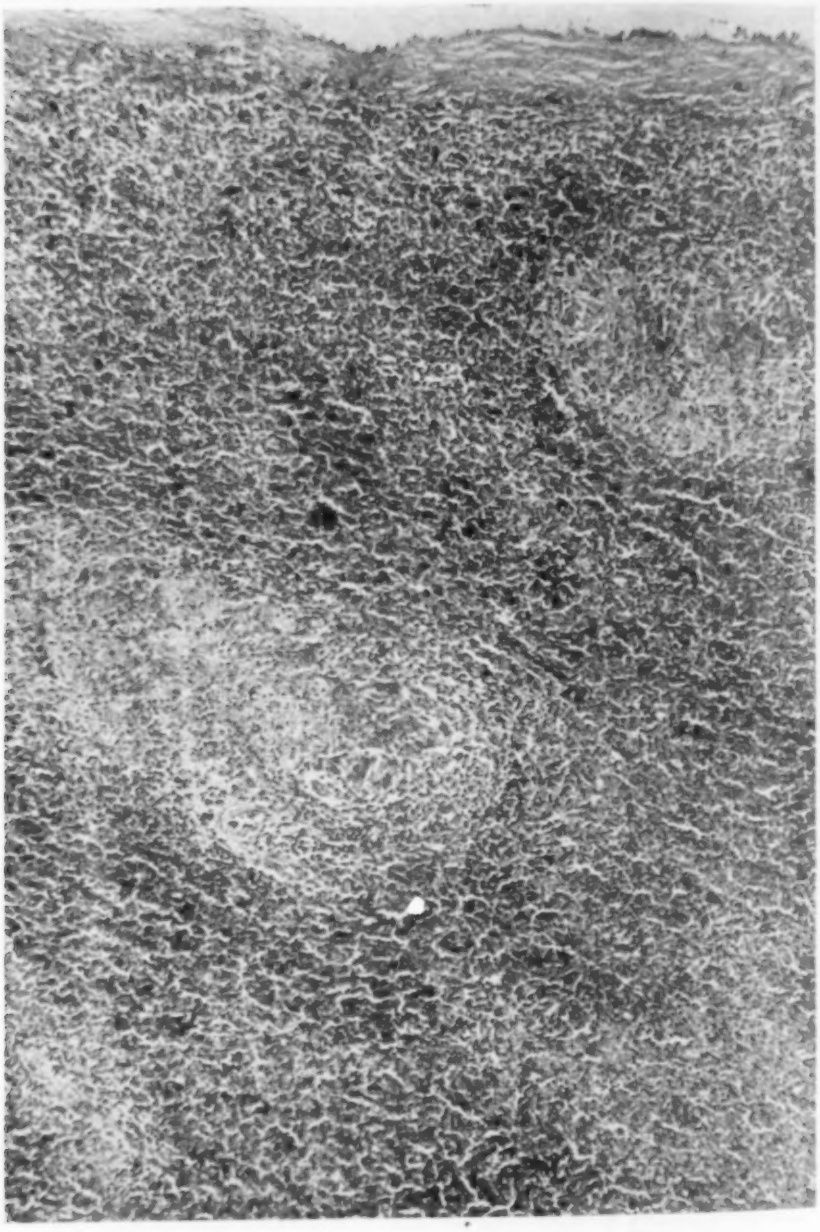

FIG. 5. Photomicrograph (×120) of section of spleen, showing submiliary tubercles. Acid-fast bacilli were demonstrated in the lesions.

The section of the coronary artery was much distorted and narrowed by a large hyaline intimal plaque with calcification.

Liver: The liver weighed 2,125 gm. On section it was a typical "nutmeg" liver. Microscopic sections showed congestion and some cloudy swelling. The chief lesion was a good distribution of miliary tubercles, which were very clear-cut and typical. No larger lesions were found in four sections (figure 4).

Spleen: The spleen weighed 300 gm. It was soft and congested. Microscopic sections showed congestion and many characteristic miliary and submiliary (or early conglomerate) tubercles (figure 5). Many acid-fast bacilli were demonstrated in the lesions. Cultures from the spleen were positive for *Mycobacterium tuberculosis.*

Kidneys: The left kidney weighed 240 gm., the right 200 gm. The cortical surfaces were finely pebbled and rather pale. On section they showed considerable narrowing of the cortices but clear differentiation between cortex and medulla. The pelves were normal. Microscopic sections showed only granular degeneration of the cells of the tubules. No tubercles were found.

Adrenals: The sections showed a small conglomerate tubercle in the cortex of one adrenal.

Other organs were not noteworthy either grossly or microscopically.

Pathological Diagnoses: (1) Arteriosclerotic heart disease; (2) atherosclerosis of coronary arteries with marked insufficiency; (3) chronic organizing pneumonia; (4) acute miliary tuberculosis of lungs, peribronchial lymph nodes, liver, spleen and adrenal; (5) benign arteriolar nephrosclerosis.

Discussion

Although proof is lacking that the administration of cortisone contributed to the development of acute miliary tuberculosis in this patient, such a situation remains a strong possibility. The small size of the tubercles would seem to indicate that they developed some time after the first course of cortisone was started. Their maximal age is estimated at approximately eight weeks. The hormone was given more than three months before death. The tubercles were so small that they were evident neither in repeated roentgenologic examinations of the chest nor in the gross specimens at autopsy. Certain clinical features of this case were suggestive of periarteritis nodosa, and it was on this basis [7] that the drug was given. Our experience would seem to indicate that the administration of cortisone to patients with undiagnosed febrile illnesses should be avoided.

The death of our patient was undoubtedly due to arteriosclerotic heart disease. Aside from its possible effect upon the unrecognized tuberculous process, the use of cortisone in this case was possibly ill-advised for other reasons. The water and sodium retaining properties of the drug, its hypertensive effect in occasional patients, its ability to raise serum cholesterol [8] and its action in producing a state of hypercoagulability of the blood [9] might contraindicate its use in a patient known to be suffering from severe coronary arteriosclerosis. That at least the first of these factors was of some importance in the present case is evidenced by the development of edema of a degree to require the use of mercurial diuretics, and by the waterlogged state of the tissues at autopsy. At no time did the clinical picture suggest congestive heart failure, however. This patient showed no significant elevation of blood pressure while receiving cortisone. Determinations of blood cholesterol and blood coagulation time were not made.

The mechanism of action of cortisone in producing a spread of tuberculosis is not known. Interference with granulation tissue formation [10, 11] would seem of primary importance. Modification of the immunologic mechanism may also be of significance, as adrenal hormones are capable of inhibiting tuberculin-type reactions.[12] Thorn believes that, through inhibition of tissue hypersensitivity, adrenal steroids may either ameliorate the severity or facilitate the spread of established tuberculous infection, and that it is not yet safe to predict which action will predominate in a given case of tuberculosis. In any event, administration of cortisone to patients with active tuberculosis should be withheld until further evidence is available.

Conclusion

A case of acute miliary tuberculosis in a patient who had received a course of cortisone ending approximately four weeks prior to date of dissemination is reported.

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PRIMARY LIPOSARCOMA OF THE MEDIASTINUM *

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LIPOSARCOMA is a rare tumor. It is still rarer as a mediastinal tumor and has never been described as invading the vena cava.

Approximately 200 cases of liposarcoma have been reported in the literature. The great majority of these occur superficially. The legs, thigh, gluteal region, popliteal space, trunk, head, neck and arms are the most common sites of involvement.[1, 2, 3] In another large group the tumors are found retroperitoneally,[4, 5] perirenally,[6, 7] and intra-abdominally.[8] In addition, liposarcoma has been described as originating in bone,[9, 10, 11, 12, 13] meninges,[14] spermatic cord,[1] breast,[15, 16] vulva [17] and common bile duct.[1] Doubtful cases are reported arising from the uterus and stomach.[1]

To date, the literature in the English language contains reports of only four cases of liposarcoma originating in the mediastinum.

Perkins and Bowers [18] in 1939 reported one case occurring in an 18 year old female whose chief complaint was cough and expectoration of greenish sputum. A roentgenogram of the chest revealed a mass in the right lower lung measuring 9 cm. in diameter. This tumor was found to be projecting from the posterior mediastinum and was removed surgically. The patient apparently made an uneventful recovery. The tumor was encapsulated and no metastases were seen.

The authors, in their discussion, stated that they had observed two other cases of mediastinal liposarcoma; one originated in the mediastinum but was inoperable when explored, the other at autopsy showed nodules in the lungs and mediastinum.

Narr and Wells [19] in 1933 described an intrathoracic myxolipoma in a 33 year old male. The tumor was entirely encapsulated except for its attachment to the mediastinum. There were no metastases to the lungs or mediastinal lymph nodes. This case was probably one of liposarcoma which had undergone myxomatous degeneration.

Joske,[20] in the *Medical Journal of Australia* in 1944 related the case of an 18 year old male who was discovered to have a posterior mediastinal tumor on a routine chest examination. At operation a liposarcoma, 4 by 3 by 2 inches, was easily separated from the pleura but was found to have infiltrated the intercostal muscles laterally. The patient was given postoperative irradiation. The outcome was not reported.

In 1942, Ackerman and Wheeler [21] reported a 50 year old female who developed orthopnea, dyspnea and a nonproductive cough following an upper respiratory infection with pleurisy. Signs of consolidation were present and the roentgenogram revealed obliteration of the left thorax. Before further diagnostic studies could be completed the patient died. At necropsy, the entire left chest was filled with a soft tumor mass which was lobulated, encapsulated, and did

* Received for publication September 24, 1949.

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not invade the lung or regional lymph nodes. The tumor was found microscopically to have invaded the small blood vessels.

Virchow in 1857 reported the first histopathologic studies of liposarcoma.

Caldwell and Zinninger [14] noted that three types of liposarcoma were described in the early literature: (1) lipomyxosarcoma, a liposarcoma which has undergone myxomatous degeneration; (2) lipoma with sarcomatous degeneration; the tumor does not arise from fatty tissue but from fibrous tissue stroma, and (3) liposarcoma, which arises from fatty tissue and tends to become encapsulated but may extend locally and even metastasize.

Probably a few liposarcomas develop from preëxisting lipomas, but it seems probable that the great majority are malignant from their very beginning.

Geschickter [22] has described the variable microscopic picture of liposarcoma. The predominating malignant tissue either resembles a fascial sarcoma with compact spindle cells or shows numerous immense tumor giant cells with degenerating nuclei and a large amount of foamy cytoplasm. Surrounding these malignant areas are islands of embryonic fat, adult fat and thick myxomatous stroma. Frequently a small cell resembling a plasma cell or fetal cartilage cell is seen. Whether this is a forerunner of a large foam cell is not known.

Ackerman and Regato [23] have pointed out the fact that the tumor can be well differentiated, resembling embryonal fat, or that it may have bizarre lipoblasts, many of them giant in size. Quite frequently the nucleus is compressed to a crescentic shape by the cytoplasmic fat. In certain other cases, the lipoblasts have a central nucleus with very foamy abundant lipoid containing cytoplasm. Grossly, the tumors tend to show convolutions which crudely resemble cerebral cortex. In the depth of these convolutions are fine lacy networks of blood vessels. Areas of necrosis, hemorrhage and mucoid degeneration are common.

Liposarcomas may occur at any age. Congenital cases have been reported.[24] However, they occur chiefly in patients of middle age and affect both sexes equally.

The tumors are usually single, but multiple tumors have been described.

Ackerman [25] reports one patient with primary tumors arising from subepicardial, mediastinal, mesenteric, peritoneal, retroperitoneal, subcutaneous and bone marrow fat.

One of the more interesting features of liposarcoma is the fact that the tumor may grow very slowly and remain relatively asymptomatic for years. Then the growth of neoplasm is suddenly accelerated and clinical manifestation becomes evident. Trauma has been found to play a very minor rôle in this sudden enlargement.

The tumors are encapsulated; therefore, they do not suggest malignancy. However, after shelling out these neoplasms, they will invariably recur locally. Local recurrences may occur a number of times before a fatal metastasis develops.

Pain is seldom a prominent symptom and, when present, is usually due to pressure or hemorrhage.

It has been estimated that the average duration of symptoms, from the first complaint until metastases are known, is 10 years.

Liposarcomas are frequently found in kidney tissues, and many of these are associated with tuberous sclerosis.[26, 27]

The tumor will metastasize, but this is usually a late manifestation. The most common sites for metastases are the central nervous system, lungs and liver.

The question of their radiosensitivity varies, some authors [28, 29, 30] claiming good results with irradiation, and others none. Probably the best results are obtained in those tumors that are superficially and easily accessible.

Case Report

A 57 year old white male factory worker entered Hurley Hospital on August 21, 1947, complaining of redness and swelling of the face of one week's duration. He stated that he had always been in excellent health until two months prior to admission, when he developed distressing pain over the anterior chest superficially which required codeine for alleviation. No history of dysphonia, dysphagia, dyspnea, cough or stridor was elicited. The past history and family history were essentially noncontributory, except for a history of substernal thyroid 20 years ago.

Physical examination revealed a well developed, well nourished white male who did not appear acutely ill. However, a marked lividity of the face and edema of the neck, face, chest and arms were most obvious. The jugular veins and the superficial veins of the face, neck, and upper thorax were quite distended especially upon recumbency. The superficial venule enlargement around the neck produced the characteristic "Stokes' collar," indicative of superior vena cava obstruction. There was no evidence of cervical or generalized lymphadenopathy. The trachea was in the midline and no tug was noted. The heart was normal in all respects. Both radial and ulnar pulses were equal and palpable. There was no abnormality of the blood pressure in either arm; the recorded pressure was 122 mm. Hg systolic and 84 mm. diastolic. No edema of the lower extremities was noted at this time.

Although the lungs were clear to auscultation and percussion, fluoroscopy of the chest revealed a prominent superior vena cava and a tumor mass, 3 by 5 by 2 cm., in the superior mediastinum at the level of D4 and D5, which caused only anterior displacement of the trachea and esophagus. The mass did not show any expansile pulsations and did not shift on deglutition. No erosion of the vertebral bodies was noted.

Venous pressure in both antecubital veins was 30 cm. of water. (Normal is 10 cm.)

Laboratory studies were all within normal limits, including complete blood count, urinalysis, sedimentation rate, basal metabolic rate, Kahn and blood cholesterol.

The patient refused to have an exploratory thoracotomy and left the hospital against advice on August 28, 1947.

He returned on September 11, 1947. The previously described edema had increased in severity. He was seen in consultation by the surgical service, who felt that thyroidectomy was indicated. A radical thyroidectomy was performed on September 15, 1947, since malignancy of a substernal thyroid gland was suspected by the surgical staff. The pathologic report of the thyroid gland was negative for malignancy.

Thyroidectomy did not alleviate the partial superior vena cava obstructive symptomatology. Because of the development of orthopnea, dyspnea, boring oppressive substernal pain, and increasing edema of face, neck, thorax and both forearms, the patient was transferred to the medical service, where deep roentgen-ray therapy was advised. It was felt that this approach would be both a diagnostic and a therapeutic procedure.

After 10 days of deep roentgen-ray therapy in September, 1947, there was initially a rapid disappearance of the superior vena cava obstructive symptomatology. The patient was discharged and he returned to his former occupation. He was seen by one of us (H. M. G.) at frequent intervals for subsequent examinations. By January

1, 1948, the circumference of his neck had decreased from 18.5 inches to 16 inches. The enlarged veins and edema had completely disappeared.

However, in spite of the clinical improvement, repeat fluoroscopy of the chest revealed a new mass in the left thorax, lateral and posterior to the tip of the left ventricle in the posterior mediastinum. This measured 4 by 6 by 4 cm. The originally described superior mediastinal tumor had not changed in size.

The development of severe, distressing migratory pain in the back and both thighs necessitated a return to the hospital on January 13, 1948. Roentgenograms of lumbosacral spine, pelvis, both lower extremities and intravenous pyelograms were negative for pathologic lesions. Repeat fluoroscopy of the chest revealed that the previously described tumor lateral to the left ventricle in the posterior mediastinum had increased in size and was now 9 by 9 by 12 cm. It was also markedly lobulated, suggesting malignancy. The opinion of the radiologist was that the mass in the superior mediastinum was a malignant tumor with regional metastasis in the posterior mediastinum.

Two firm subcutaneous nodules were noted over the xiphoid portion of the sternum and apparently had an osseous attachment to the sternum. These nodules had appeared in January, 1948. They measured 2 by 8 by 1 cm. They were biopsied on January 14, 1948.

The pathologic report of the above tumor was most revealing. Microscopically, the section consisted of solid masses of cells which varied from pure fat to signet-ring cells, all in a compact mass without intervening stroma. The most cellular areas were solid purple, small spindle-shaped cells, rather uniform in size. Separate stains for fat revealed this tumor to be abundantly supplied with fat, even in the most cellular areas. It was felt by the consulting pathologists * that this tumor was a metastatic liposarcoma, probably primary in the superior mediastinum from the clinical evidence.

The patient's course was steadily downward from this point, in spite of subsequent deep roentgen-ray therapy and general supportive measures, including repeated blood transfusions, antibiotics, indwelling catheter and intravenous teropterin therapy. Surprising subsidence of the severe edema of the right leg occurred during teropterin therapy. Progressive anemia, dyspnea, urinary incontinence, orthopnea, generalized subcutaneous nodules and general debility characterized the terminal stage of the illness. He died on June 17, 1948.

Necropsy Findings. The subject was a 178 cm. white male, weighing an estimated 160 pounds. Examination of the head revealed six firm nodules beneath the scalp, varying from 3 to 7 cm. in diameter. Examination of the neck revealed a 17 cm. thyroidectomy scar. There were numerous firm nodules in the subcutaneous tissue overlying the anterior and posterior thoracic cage. One of these nodules had a central ulceration from which neoplastic tissue protruded. A biopsy scar was noted over the chest anteriorly.

Midline incision revealed that the panniculus was practically absent. Beneath the skin, subcutaneous nodules were seen adhering to the sternum and ribs. These nodules varied from 3 to 5 cm. in diameter. They were firm in consistency.

The sternum was easily removed, revealing numerous nodules in the anterior mediastinum. They were yellow in color and quite soft. All these nodules were encapsulated. Although the diaphragms were at the normal level, the veins on both the inferior and superior surfaces of the diaphragm were very prominent, indicating a collateral circulatory response. There were numerous nodules varying from 2 by 4 by 2 cm. to 4 by 6 by 4 cm., in the pleural space of the left thorax. Most of the pleural cavity was obliterated bilaterally by dense adhesions.

The most obvious abnormality was a soft yellow tumor, measuring 12 by 12 by 8 cm., located in the posterior mediastinum and projecting anteriorly into the middle

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mediastinum lateral to the apex of the heart. A second tumor of the same characteristics was found in the superior mediastinum at the level of D4. This tumor extended inferiorly into the posterior mediastinum and anteriorly into the middle mediastinum. It measured 7 by 6 by 4 cm. The tumor masses did not invade the vertebral column, aorta, thoracic duct or vagi nerves. The esophagus and trachea were displaced anteriorly by the tumor but not invaded. Both the superior vena cava and azygos veins were invaded by the tumor and compressed in some areas. The neoplastic tissue extended within the superior vena cava a distance of 4 cm. into the right auricle. The greatest diameter of this projection into the right auricle was about 4.5 cm. Grossly it appeared that the superior vena cava had been completely obliterated at one time and was now partially recanalized.

The heart was normal in size and somewhat flabby in consistency. The endocardium was normal in all respects. There were no cardiac or pericardial metastases. The coronary arteries were normal.

The lungs were dark, bluish red in color, mildly edematous; the right lung weighed 475 gm., the left 380 gm. No areas of consolidation or metastases in either lung were noted grossly.

The peritoneum was smooth and shiny. The liver was enlarged, weighing 2,040 gm. The parenchyma cut with ease, revealing metastatic tumor nodules varying from 2 cm. to 12 cm. in diameter. The spleen was normal and the kidneys were quite firm. The right kidney weighed 200 gm., the left 225 gm. There was no evidence of renal metastases in the left kidney, but two yellow nodules were present on the surface of the right kidney.

In the lumen of the inferior vena cava at the lumbar level was another mass of neoplastic tissue measuring 10 cm. in length. The lumen was not completely occluded. Distal to this mass was an organized thrombus in the inferior vena cava extending into the left renal vein and both common iliac veins. Immediately posterior to the inferior vena cava was a tumor mass, measuring 8 by 5 by 3 cm., adherent to the lumbar vertebrae and nerve roots. There was one small mass anterior to the neck of the bladder on the floor of the pelvis, measuring 2 by 3 by 2 cm.

The adrenals, bladder, prostate, pancreas and gastrointestinal tract were within normal limits and showed no evidence of malignancy.

Microscopic Examination. The primary tumor in the superior mediastinum consisted of solidly cellular, spindle-shaped cells and cells forming adult fat. Separate stains for fat revealed that the tumor was abundantly supplied with fat even in the most cellular areas. Special stains showed no cholesterol or cholesterol esters. The extensive neoplastic invasion of both superior and inferior vena cava consisted of tumor and inflammatory clot.

The previously described metastatic lesions in thorax, liver, retroperitoneal area, azygos vein and right kidney were microscopically found to be characteristic of liposarcoma.

Liver: Extensive metastases. Fatty infiltration and parenchymatous degeneration.

Lungs: A patchy purulent bronchopneumonia. Moderate anthracotic pigmentation. Multiple metastatic nodules.

Kidneys: Two metastatic nodules in right kidney and chronic passive congestion with marked parenchymatous degeneration of both kidneys. Pelvis and ureters were negative. Organized thrombus of inferior vena cava and left renal vein.

Gastrointestinal tract: Essentially negative.

Spleen, adrenals, pancreas: Essentially negative.

Prostate: Moderate glandular hypertrophy.

Final Anatomic Diagnosis. (1) Liposarcoma, retroesophageal portion of su-

perior mediastinum. (2) Metastases (sarcomatosis): *a.* Pulmonary, hepatic, renal, subcutaneous, retropleural, retroperitoneal and lymphatic. *b.* Tumor embolization of superior vena cava, inferior vena cava, and azygos veins. (3) Thrombus, organized —inferior vena cava left renal vein and both common iliac veins. (4) Circulation, collateral, extensive—vertebral, superior and inferior epigastric and internal mammary veins. (5) Cachexia, neoplastic. (6) Ischemic nephrosis, moderate. (7) Surgical absence of thyroid gland.

Discussion

A comparatively high percentage of intrathoracic tumors either originate within the mediastinum or invade the mediastinum from surrounding structures or organs. Because of the many varied tissue components in the mediastinum, it may be the site of almost any type of neoplasm.

The most common benign tumors in the mediastinum are dermoid cysts and neurofibroma; the most common malignant tumors, lymphoblastoma and lymphosarcoma. However, from time to time, primary tumor of the mediastinum presents an unusual clinical and pathologic picture which confuses the clinician as to treatment and the pathologist as to classification. The presented case falls into the latter category.

Liposarcomas are extremely rare tumors. Perhaps their rarity may be explained on the basis that fat is an inactive tissue with very little growth capacity. However, Haagensen and Krehbiel [31] have experimentally produced liposarcoma in mice and guinea pigs by the subcutaneous injection of 1:2 benzopyrene. Apparently the stimulating action of benzopyrene was so great that it could produce malignant change in this relatively inactive tissue.

It is a known fact that all neoplasms of the mediastinum, even though benign, are a threat to life. They have the inherent potentiality of becoming malignant and, because of the limited size of the mediastinum, have little space for growth without encroaching upon or invading vital structures.

In the present case, the superior vena cava and azygos veins were not only compressed, giving the superior vena caval obstructive syndrome, but also invaded. The tumor apparently grew within the superior vena cava to the heart and extended directly into the right auricle. Invasion of this structure has not been previously attributed to liposarcoma.

It is most interesting to note the comparative well being of the patient until the terminal stage of his illness, considering the extensive metastases noted at necropsy. This is most characteristic of mediastinal liposarcoma, as opposed to other malignant neoplasms of the mediastinum.

A unique feature of the cited case was the clinical improvement and disappearance of the superior vena cava obstruction following deep roentgen-ray therapy. At necropsy, the superior vena cava appeared to have been recanalized through neoplastic tissue. One might speculate that deep roentgen-ray therapy was responsible for the partial recanalization of the superior vena cava. This was a most unusual finding, considering the extensive metastatic involvement of the mediastinum.

The occurrence of subcutaneous metastases secondary to primary mediastinal liposarcoma is unusual. To our knowledge, this is the only case cited in the literature.

Summary

Another case of primary liposarcoma of the mediastinum is reported, with a general review of the literature. The outstanding features of this case are those of superior vena cava obstruction, with subsequent invasion of the vena cava and extension into the heart. Apparently under deep roentgen-ray therapy, the neoplastic tissue within the superior vena cava partially recanalized, with alleviation of the vena caval obstructive symptomatology. Since this was almost a unique occurrence in an uncommon neoplasm, it was felt that this case should be reported.

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RECOVERY FROM REFRACTORY DIABETES INSIPIDUS ASSOCIATED WITH NARCOLEPSY *

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THE hypothalamus has been suggested as the anatomic locus for many diseases and syndromes, two of which are narcolepsy and diabetes insipidus. Evidence that diabetes insipidus originates here is convincing. It has been established both clinically [3] and experimentally [10, 20] that this syndrome results from a lesion of the hypothalamico-hypophysial tract. Specifically, bilateral destruction of the supraoptic nuclei produces diabetes insipidus although high section of the infundibular stalk may do the same. Removal of the posterior lobe of the pituitary gland does not result in water imbalance. In sleep disturbances of the narcoleptic type we are less certain of the etiology, but scores of modern writers on the subject have been influenced by a mass of experimental and indirect clinical evidence to accept the hypothalamus as a fundamental regulator of sleep rhythm. Some of the more cogent contributions to this belief are by Fulton and Bailey,[12] Economo,[9] Hess,[14] Rowe,[22] Ranson [19] and Kleitman.[16]

The two syndromes may occasionally occur together in certain organic brain diseases, notably third ventricle tumors, or after operations for basal tumors.[1, 12] Most cases of narcolepsy are considered cryptogenic, and some cases of diabetes insipidus fall into the same category. It is impractical to review completely the literature on these two subjects since it comprises hundreds of articles, but insofar as we can ascertain it contains no clear-cut case of the cryptogenic type of both disease patterns in the same individual. In fact, this singular lack of concomitance seems to confute a common anatomic seat for these two syndromes.

Daniels,[5] after a most comprehensive survey of narcolepsy, concludes that the two syndromes do not co-exist. Following a review of the literature and a study of 147 case records of the Mayo Clinic, he states, "So far as I know, no case of narcolepsy associated with diabetes insipidus has been reported, although I have heard of a young girl who passes large amounts of urine. Both Pfanners' and Henneberg's patients were said to have mild polyuria, although in Henneberg's case the volume of a 24-hour specimen amounted to only 2,400 cc. One of Red-

* Received for publication November 2, 1949.
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lich's patients had moderate polyuria and polydipsia. Three patients seen in the (Mayo) Clinic complained of frequency of urination and increased thirst, but only one of these appeared to be passing an excessive amount of urine. Of seven other patients who, like Fulton and Bailey's patient, complained of increased urination, one, whose polydipsia was mainly nocturnal, excreted 1,500 cc. between 7 p. m. and 7 a. m. The volumes of specimens of urine submitted by the other six were well within normal limits. Two other patients excreted rather large amounts."

The modern literature presents three other cases concurrent with narcolepsy with suggestive alteration in water balance, but lacking clear-cut diagnostic evidence of diabetes insipidus. Case 1 of Shapiro's [23] was a male with onset of narcolepsy at age 11. At 17, he complained of excessive fluid intake and weight gain, but the case report failed to mention specific gravity or output of urine. Speirs and Speirs [24] noted that one of their cases of narcolepsy also had polyuria with the day/night ratio of frequency 9:2. This changed to 3:0 with ephedrine therapy. There was no polydipsia or unusual dilution of urine. In case 2 of Hall,[13] the patient had polydipsia and weight gain without untoward urinary symptoms.

The following case, illustrating simultaneous cryptogenic narcolepsy and diabetes insipidus, is apparently unusual and may indeed be the first such case recorded. Further provocative aspects of this study were (1) refractoriness of the diabetes insipidus to pituitrin therapy, and (2) a six years' spontaneous recovery from diabetes insipidus after a febrile episode.

Case Report

The patient, age 58, white, married, a machinist, was admitted to the medical service of the Royal Victoria Hospital on April 2, 1943, complaining of troublesome sleepiness for three years, and excessive thirst and urination for one month.

Present Illness. Until the gradual onset in 1940 of symptoms which induced him to seek hospital treatment in the spring of 1943, the patient's health record was consistently good. One year before admission he changed from stimulating work as his own boss, with irregular hours and a full schedule, to the decreased pressure of a salaried routine job with regular hours. The typical symptom of narcolepsy then became acute. He was subject to irresistible attacks of sleep after meals, when sitting, reading, riding or doing routine work. He could fight off attacks if active and stimulated and on his feet. The spells of sleeping lasted from two to 30 minutes, depending upon whether or when he was aroused. The only prodromal symptom was heavy eyelids. He slept lightly and awoke easily but often felt drowsy and irritable when wakened. Attacks were not variable according to season or weather. In the first year of the present illness, he experienced his initial cataplectic type of attack. Since he seldom if ever laughed heartily, his "weak" spells usually were precipitated by anger. He was prone to vehement argument, and when his temper was aroused "got as limp as a rag" and had to slump in the nearest seat for five to 10 minutes before his strength (and temper) returned to normal. There was no clouding of consciousness, or other evidence suggestive of epilepsy. He did not present the correlated symptoms of the narcoleptic syndrome, sleep paralysis, sleep hallucinosis, sleep talking or personality variations. He described stereotyped dreams, both at night and during narcoleptic attacks, always with himself in a familiar home or work setting, engaged in a preferred activity such as reading or doing a piece of precision tooling. He gave no history of headaches, ocular symptoms, excessive appetite, alteration of sexual function, unusual reaction to heat or cold, dermographia or epistaxis.

The second major symptom, frequency of urination, developed suddenly one month before admission. The patient contracted a brief upper respiratory infection with fever, cramping paralumbar pains, and slowing of the urinary stream, with hesitancy. One day later polyuria, polydipsia and dry mouth developed. He continued voiding nearly every hour, day and night, until admission. There was no dysuria, hematuria or weight change.

Family History. His mother had died at age 66 in an automobile accident, his father at age 64 from carcinoma of the lung, a sister in infancy. Of his four living siblings, two brothers and a sister were well and a third brother was afflicted with bronchial asthma. There was no other significant family history.

Past Medical History. The patient had had the usual childhood diseases, not including scarlet fever. No other illnesses, operations or accidents occurred. There had been a steady weight gain of 20 pounds in the past 20 years. Recently he had noticed a slight bilateral decrease in hearing acuity; other routine history by systems and psychosomatic inquiry was essentially negative.

Psychiatric Evaluation. Discussion of the patient's birth, childhood, social adjustment, education, occupation, avocations, religion and sexual and marital history disclosed no gross deviations from the normal range of behavior or development. He had always been an individualist, a little wary of emotional involvement with other persons, ambitious, too defensive of his rights and apprehensive about being imposed upon. Now that he was older he feared getting into arguments that might lead to physical violence, therefore his anger reactions were more associated with surface anxiety than previously. He continued to show ability, drive and accomplishment.

Psychometric Studies. Rorschach test: R–12, W–5, D–6, d–1, FM–4, F–5, Fc–2, FC–1; there were a fair number of popular answers, and failure on card IX. The personality description was as follows: "Average intelligence with more than average common sense but inhibited in his own inner life by a critical attitude toward his own fantasy. Extraversial adjustments are accepted more readily. Neurotic traits are brought out when he is subjected to a combination of emotional stresses, although these are not prominent on the surface."

Bellevue-Wechsler test: verbal I.Q.—125; performance I.Q.—113; average I.Q. 119.

Shipley-Hartford: vocabulary score 35, age 19; abstraction score 16, age 12; C.Q. 68; M.A. 15.3, I.Q. 105.

Physical Examination. Well developed male, pyknic habitus, 5 feet 5 inches tall, 180 pounds, temperature 98° F., pulse 80, respirations 20. Skin: normal hair distribution; no dermographia; some hyperhidrosis of palms. Skull: no asymmetry or tenderness. Eyes: pupils round and equal, conjunctivae and corneae clear. Ears: otoscopic examination negative. Nose: no obstruction or discharge. Mouth: tongue pink and clean, gums and teeth normal. Pharynx: tonsils atrophic. Neck: no adenopathy. Chest: respiratory movements normal; lung fields clear; heart of normal size, sounds clear, pulse full and regular; peripheral vessels elastic and compressible; average blood pressure, 160 mm. Hg systolic and 88 mm. diastolic. Abdomen: moderate obesity, no enlarged organs. Genitalia: not remarkable. Rectal: slight enlargement of the median lobe. Spine: no postural defects, rigidity or tenderness. Extremities: no developmental defects, joint pathology or varicosities.

Neurologic Examination. Cranial nerves were intact. Muscular development was symmetrical; no atrophy, weakness or change in muscle tone. Coördination was good. Sensory system was intact. Reflexes were entirely physiologic. Autonomic system was negative except for palmar sweating.

Genitourinary Examination. Cystoscopic study showed a moderate median lobe enlargement with, however, only 0.5 ounce residual urine. Phenolsulfonphthalein

showed about 40 per cent excretion from both ureters. Retrograde pyelograms were entirely normal.

Laboratory Data. Hemoglobin 84 per cent (Sahli); red blood cells, 4,400,000; white blood cells 7,400; differential, polymorphonuclears 66, lymphocytes 28, monocytes 6; sedimentation rate 6 mm. in one hour. Blood Kahn test negative; non-protein-nitrogen 33.6; creatinine, 1.3; cholesterol, 214; serum sodium, 331; serum calcium, 10.5; inorganic phosphorus, 2.12. Glucose tolerance test, a.c. 92, one-half hour, 186; one and one-half hours, 184; two hours, 138; three hours, 101; insulin tolerance test, a.c. 98, 10 min. 41, 30 min. 54, 60 min. 80, 120 min. 95. Basal metabolic rate, plus 27. Cerebrospinal fluid, cells 0, protein 36, Kahn negative, Lange negative, initial pressure 200 mm. H_2O.

Roentgenograms. Skull films were entirely negative except for slight thickening of the vault, probably of no clinical significance.

Pneumoencephalogram. Both lateral ventricles were enlarged, more in the body than anteriorly; the third ventricle was well filled and showed no deformity; the fourth ventricle was normal; the cisterns were well visualized and presented no abnormality; there were prominent cortical markings, most distinct in the frontal region.

Electroencephalogram. With eight standard head leads from each side, as well as undifferentiated monopolar leads from both ears and a basal lead placed against the nasopharynx, the following records were obtained: (1) Abnormal potentials from cortical leads occurred almost entirely in the monopolar tracings and consisted of irregular low amplitude random delta activity. (2) Phase reversals were seen quite frequently at the indifferent electrodes on both sides. (This suggests a deep central origin for the abnormal discharges.) (3) Tracings from the basal lead showed a constant phase reversal of the delta wave activity at the basal electrode, which again suggests deep central origin. (4) Three and one-half minutes of deep hyperventilation produced no change. (5) There was a persistent pulse artefact in all monopolar records. (The significance of this is not known.)

Hospital Course. After a month of continued urinary distress, the patient was admitted for investigation. Results of repeated urinalyses were entirely negative except for a persistently low specific gravity, varying from 1.002 to 1.007. Response to pitressin was poor, the concentration rising to a maximum of 1.010 with three injections daily. A phenolsulfonphthalein test showed only 40 per cent excretion; therefore the genitourinary studies were done, but there was no pathologic finding. Immediately after the cystoscopy, however, specific gravity of urine improved temporarily. At this time the patient developed a febrile reaction and mental confusion, which cleared in 48 hours when sulfathiazole was administered orally. With continued aqueous hypodermic and intramuscular pitressin in oil, the urinary specific gravity increased, varying from 1.012 to 1.022. The narcolepsy was controlled with 5 mg. benzedrine three times a day. The patient was dismissed, and follow-up studies in July, 1943, four months after the onset of polyuria, revealed that the diabetes insipidus was apparently cured and pitressin was no longer necessary. Narcolepsy was still responding well to 20 mg. of benzedrine daily in divided doses.

The patient and his wife were interviewed in 1948 by Miss Emard, of the Montreal Neurological Institute Social Service staff, and the patient was interviewed by one of us in 1949. For six years he has required no therapeutic aid to remain completely free from any symptoms of diabetes insipidus. His narcolepsy continues, although it is less severe.

Discussion

This case history presents many typical features of cryptogenic narcolepsy. Insidious onset over a period of years and aggravation of sleepiness by monoto-

nous work and relaxation are trite details in the narcoleptic story. The absence of discernible neuropathology and good response to benzedrine sulfate substantiate the diagnosis.

Cataplexy is commonly associated with sudden laughter, but among the patients we have studied several have reported experiencing the same disconcerting weakness from other strong and unexpected emotional surges, such as weeping, anger, resentment, envy and selfconsciousness. This patient's flaccid spells resulted only from anger. Daniels [5] observed that patients whose chief cataplectic stimulus is anger usually do not respond similarly to laughter.

Reports from laboratory blood studies were, for the most part, normal. The blood count did not reveal the lymphocytosis and eosinophilia often found in narcolepsy. The glucose tolerance was slightly decreased and the insulin tolerance slightly increased according to the standards of Fraser, Albright and Smith,[11] but not sufficiently to clarify at all the controversial rôle of the hypothalamus in carbohydrate metabolism. In our experience most cryptogenic narcoleptics show a normal or increased glucose tolerance.[18]

The presence of diabetes insipidus in this case seems incontestably established by clinical symptoms and urinary findings. The enlarged prostate and poor phenolsulfonphthalein excretion suggested genitourinary pathology as a complicating factor, but detailed investigation ruled that out. Lack of response to pituitrin in cases of diabetes insipidus has been noted in other papers,[1, 4, 5] and apparently should not be considered a diagnostic criterion. Snell and Roundtree have indicated that diabetes insipidus following epidemic encephalitis, presumably with hypothalamic involvement, is rarely benefited by injections of pituitrin.[2] Other more complicated neural mechanisms have also been postulated. Mehes and Molitor [17] suggested the presence of a water center in the brain controlling the water content of tissues; lesions of this center might interfere with the response of the organism to pituitrin. Dreyfus,[8] and later Biggart,[4] believed that there are cell groups in the tuber cinereum on which pituitrin acts to inhibit diuresis, and that damage to this tuberal region negates the action of replacement pituitrin. Riddoch [21] also subscribed to this view. Dott [6] stated, "It (pituitrin) fails to produce any influence whatever on the condition (diabetes insipidus) if the posttuberal part of the hypothalamus is injured. It is necessary to assume not only that the secretion of pituitrin is controlled by the hypothalamus, but also that its action is potentiated by another neural mechanism."

Hypersomnolence is a symptom of dysfunction in the mammillary region of the posterior hypothalamus. Impairment or destruction in this area apparently interferes with the waking center, allows ascendancy of anterior hypothalamic control and results in vagotonia with accompanying hypersomnolence.

If ordinarily diabetes insipidus results from dampening or disruption of the anteriorly placed supraoptic nuclei and their tracts, then we might assume that narcolepsy and diabetes insipidus would occur simultaneously in the same organism only as the consequence of a relatively massive organic lesion.

If, on the other hand, diabetes insipidus which is refractory to administration of pituitrin may be related to disturbance in the medially placed tuberal region, then the coincidence of these two syndromes might have resulted from a single pathophysiologic process.

Many investigators [16] believe that the direct hormonal action of pituitrin on

the kidney tubules is a refutation of the neural hypotheses. Pituitrin is effective on the isolated, denervated kidney, which seems evidence against the existence of secondary neural pathways. Other works recommend the evaluation of other factors influencing diuresis, particularly ionic concentrations. The amounts of K and Ca and, secondarily, of phosphate in the blood profoundly affect the water-absorbing mechanism and may overbalance the action of pituitrin. Neural theorists propose that these ionic concentrations might be influenced by cell groups within the tuber cinereum.

Ionic concentrations during sleep have also been the subject of extensive research. The fall of blood calcium during sleep and narcosis has been repeatedly observed, and several workers have succeeded in producing sleep by injecting calcium into the infundibular region of the brain. This nonspecific depressant effect of calcium points to the possibility that disturbed ionic concentrations in the hypothalamus, from whatever origin, can produce sleep.

It seems advisable to mention another point concerning the refractory behavior of pituitrin. It has been noted in diabetes insipidus that pituitrin is ineffective when patients are asleep or under the influence of hypnotics and surgical anesthesia.[1, 21] This introduces the question of whether our patient's narcoleptic hypersomnolence may have inhibitively influenced the hormone. Polyuria bothered him at all hours of the day and night, whether he was awake, in a narcoleptic attack or in normal sleep. We were unable to arrive at any positive conclusion in this respect. We could not attach significance to the possibly inhibitory effects of sleep on his hormone therapy, since our patient's diabetes insipidus did ultimately respond to pituitrin and undergo remission, without any corresponding change in his narcolepsy.

We can only speculate regarding the type of "lesion" this patient presented. The clinical investigation and subsequent six-year course did not disclose anatomic lesions such as tumor, abscess and infarct. The patient's age, elevated blood pressure and poor phenolsulfonphthalein excretion might suggest a vascular lesion. However, nine years' history of narcolepsy precludes any but chronic pathology, and we have no other confirmation of cerebral arterial disease. A discrete vascular lesion of the hypothalamus, if it ever occurs, is so rare that nothing is known about it.[20] One definite "organic" lead was found in the electroencephalogram, which showed a persistent slow wave deformity from the base of the brain. In the absence of a demonstrable anatomic lesion, this abnormal electroencephalographic pattern, together with the metabolic changes, signifies an electrochemical "lesion" at the base of the brain.

Understanding of the etiology in this patient's illness is further complicated by the fact that the pituitrin-refractory diabetes insipidus not only became suddenly responsive to the hormone but also cleared completely later, while the narcolepsy continued. This might be attributed to two factors: (1) Other cases of diabetes insipidus, and also cases of narcolepsy,[7, 20] have improved or been completely cured by pneumoencephalogram or by simple lumbar puncture. We do not know that adequate explanation has ever been given for this "mechanical" effect on the hypothalamus. (2) The other possible therapeutic agent was the sudden febrile reaction following cystoscopy. That it affected the brain was manifest in the patient's confusion. It is interesting that the diabetes insipidus was apparently precipitated also by a febrile reaction. One might predicate a

functional change due to a physical-chemical alteration. This is compatible with the concept of a physiologic rather than an anatomic "lesion."

Summary and Conclusions

1. A case history of simultaneous diabetes insipidus and narcolepsy has been presented. The diabetes insipidus was initially refractory to pituitrin therapy, but after (1) a pneumoencephalogram and (2) an acute febrile course following cystoscopy, the hormone injections suddenly became effective. Within a few weeks the patient was completely free from symptoms of diabetes insipidus and has remained free for six years without any treatment. The narcolepsy has persisted unchanged except for symptomatic relief obtained from benzedrine sulfate.

2. Positive findings included a basal metabolic rate of plus 27, a suspicious glucose tolerance curve and a slow wave deformity in the electroencephalogram from the base of the brain.

3. The findings and clinical course in this case prompt one to conclude that pituitrin-refractory diabetes insipidus may be due to a hypothalamic disturbance rather than to a pituitary abnormality.

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REINFECTION BRUCELLOSIS: A REPORT OF TWO CASES*

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Our knowledge of immunity in human brucellosis is fragmentary. That an active acquired immunity develops after infection with Brucella is suggested by the observation that persons who have recovered from the disease usually fail to show clinical evidence of reinfection in spite of probable repeated exposure.[1] Whether persons known to have had mild or subclinical brucellosis also have some immunity is more difficult to determine. If a person with a history of probable exposure to the organism and a positive brucellergin skin test is considered to have had an inapparent or mild Brucella infection at some time in the past, then it is important to know whether such a person has a greatly increased resistance to further infection with Brucella. There are few published reports of brucellosis in such individuals. Meyer[2] has reported a fatal case which occurred in a man with a positive skin test. This illness was thought to have been the result of the ingestion of a large quantity of a virulent Brucella culture. Howe et al.[3] noted that one of their patients had shown a positive skin test prior to illness. Because this person had received a series of intradermal injections of vaccine, it is possible that the vaccine caused the hypersensitivity. Inasmuch as the positive skin test was found only 60 days prior to the onset of an acute illness, there is also the possibility that the patient was tested during the quiescent period of the disease.

The present paper presents two cases in which there is epidemiologic, clinical and serologic evidence of reinfection brucellosis.

Case Reports

Case 1. A 31 year old male research worker and veterinarian reported to the hospital on July 12, 1948, complaining of a sore throat, fever, headache and fatigue of 10 days' duration. The patient was known to have been involved in two laboratory accidents, one on May 11, the second on June 2. In the latter accident he was defi-

*Received for publication December 10, 1949.
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nitely exposed to *Brucella suis*. The patient remained well until July 2, when he complained of aches and muscle pains, slight headache and fatigue, and noticed a mild gingivitis. A small herpes-like ulcer appeared on the mucous membrane of the lower lip. During the following four days there was a slight increase in severity of the original symptoms. At this time the patient was examined by a dentist and received treatment for his gingivitis. Blood cultures for Brucella were taken on July 6 and 7.

Although the patient felt better during the next several days, on July 10 he developed a sore throat, headache, weakness, chills and fever. These symptoms persisted and he was hospitalized on July 12.

A review of his medical and occupational history was pertinent only in regard to his possible prior exposure to Brucella. He was born and reared in an urban center. He had never lived or visited in the country and had never knowingly drunk raw milk. From 1936 to 1940 he had attended veterinary school, where it is highly probable that he was actually exposed to Brucella. At that time the cattle upon which the students did their experimental surgery and dissection had been condemned because of Bang's disease. No special precautions were observed to prevent infection.

His immunologic record showed that he had a positive skin reaction to both brucellergin and a bacterial antigen 19 months before the first accident on May 11. The positive skin test plus the history of exposure were considered to be good evidence of a previous subclinical Brucella infection. His Brucella agglutination test at the time of the first accident was negative.

The positive findings on physical examination were limited to the oropharynx and related structures. There was a moderate diffuse inflammation of the soft palate and tonsillar pillars. On the left tonsillar pillar there were two small shallow ulcers. There were similar single ulcers present on the buccal surfaces of the upper and lower lips and on the left lower buccal gingiva. The anterior cervical nodes were slightly enlarged and tender bilaterally.

A culture taken from the gingival ulcer yielded many streptococci but no Brucella. A throat culture showed the presence of beta hemolytic streptococci in moderate numbers. A therapeutic trial of penicillin was started and then discontinued after 72 hours.

The patient continued to be acutely ill, with daily temperature elevations as high as 104° F. Headache and generalized aching were present. On July 17 the patient complained of dull pain in the upper abdomen and had a moderate diarrhea. There was moderate tenderness to deep palpation, but neither the liver nor the spleen was felt.

On July 18, *B. suis* was recovered from blood cultures secured at the onset of illness. The patient was observed for four days, during which time he continued to be acutely ill without remission of fever or symptoms. The agglutinin titer on July 19 was 1 : 200.

On July 23 the patient was started on a course of combined streptomycin and sulfadiazine, in the dosage recommended by Spink and associates.[4] Streptomycin, 0.5 gm., was injected intramuscularly every six hours, and sulfadiazine was given in the usual oral dosage of 1 gm. every four hours.

The patient experienced moderate subjective improvement within 24 hours. On the third day of therapy there was a decline in the fever and the patient felt remarkably well except for moderate weakness. Streptomycin was given for a total of 14 days and sulfadiazine for 21 days. After two weeks of convalescence the patient was perfectly well. His agglutinin titer on August 30 was 1 : 800. During the next 12 months there was no return of symptoms.

A graphic summary of this case is presented in figure 1.

Case 2. A 45 year old research supervisor was hospitalized on December 18, 1948, with complaints of headache, muscular aches, chills and fever. The patient had worked with *B. suis* for a single afternoon about five weeks prior to the onset of his

symptoms. He had been perfectly well until December 14, when he noticed some generalized aching and malaise, mild headache and a slight fever. One day later he had a severe shaking chill, followed by fever and profuse perspiration. At this time his headache became more severe and was most prominent in the right temporal region. Chills and fever were again present on the night of December 17, and the patient was admitted to the hospital on the following day. A review of his past history revealed no illness suggestive of brucellosis. The patient stated that in childhood he had consumed large quantities of raw milk obtained from cows in an area where Bang's disease was endemic. Since that time he has drunk only pasteurized milk.

A skin test with brucellergin, done April 11, 1945, 26 months before his hospitalization, was positive, and it was felt that this indicated a subclinical Brucella infection incurred in childhood. A Brucella agglutination test performed on November 3 showed a titer of 1 : 100.

The physical examination revealed no abnormal findings except a temperature of 103.4° F.

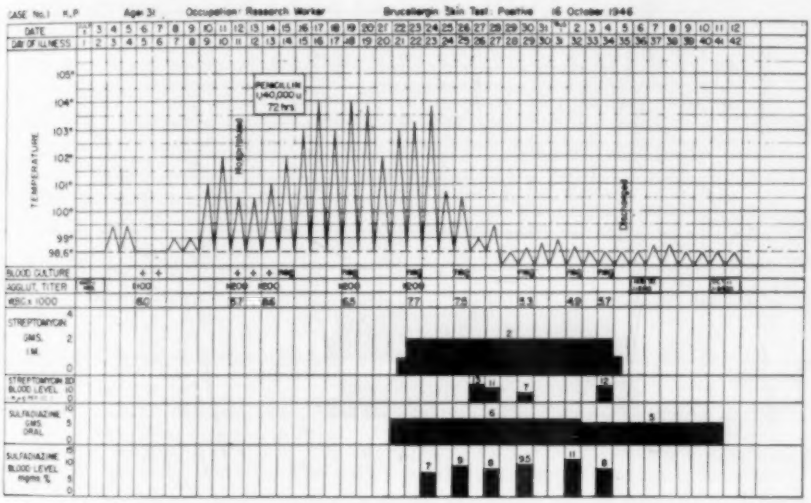

FIG. 1. Acute brucellosis due to *Brucella suis* in a known brucellergin skin test positive person. Successfully treated with combined streptomycin and sulfadiazine.

Blood cultures and animal inoculation of blood were negative for Brucella. The agglutination titer was 1:320 at this time (December 17).

A presumptive diagnosis of brucellosis was made and the patient was started on a course of combined streptomycin and sulfadiazine. Two grams of streptomycin and 6 gm. of sulfadiazine were given daily for 14 days.

During the first week of hospitalization and therapy there was a gradual decline in the degree of fever. Severe occipital headaches were complained of and did not subside until after six days of therapy.

On the eighth day of therapy the patient developed a generalized maculopapular rash which disappeared in four days. Beginning on the tenth day of therapy a daily increase in temperature was noted. With the completion of 14 days of therapy, both drugs were discontinued and the temperature immediately dropped to normal. While it is likely that this fever was the result of a drug sensitivity, no effort was made to determine which drug was the causative agent.

The patient was afebrile during the last seven days of hospitalization. Convalescence during hospitalization was slow in that moderate activity caused excessive fatigue.

The agglutination titer was 1 : 800 on both the twenty-fourth and the thirtieth days of illness.

The patient, examined 60 days after discharge, stated that he had had two minor febrile episodes accompanied by mild generalized aching and excessive fatigue. Blood cultures taken during one of these episodes were negative for Brucella. The patient's present status is unknown.

A summary of this case is shown in figure 2.

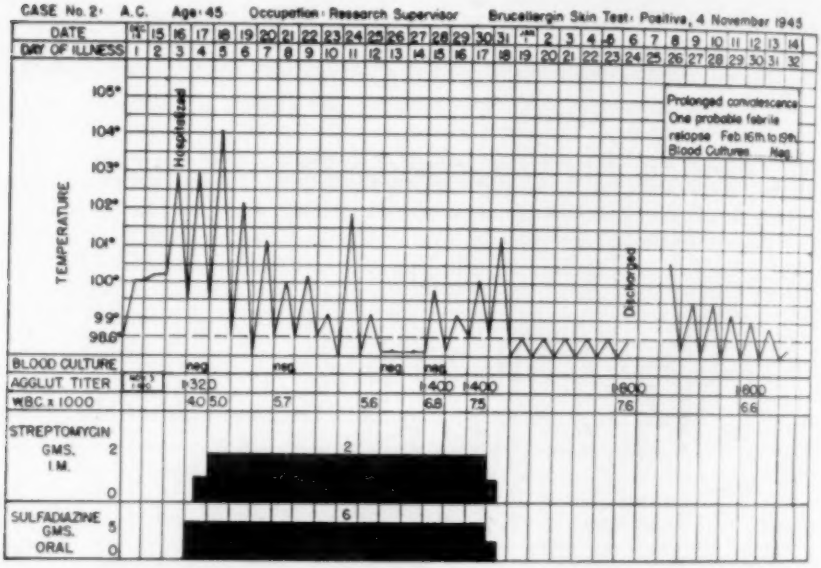

FIG. 2. Acute brucellosis in a known brucellergin skin test positive person. Treated with combined streptomycin and sulfadiazine. Two mild relapses following therapy.

DISCUSSION

The basis for believing that each of these two persons had subclinical brucellosis prior to the acute illness in each instance is the history obtained regarding probable exposure and the presence of a prior positive skin test. All the data available indicate that cutaneous hypersensitivity to brucellergin in man is specific,[5] may be of long duration [5, 6] and is not engendered by ingestion [7] or injection [8] of dead bacteria. Therefore, it is generally agreed that a positive skin test indicates either a prior or a latent Brucella infection.

That the acute illness of these two patients was brucellosis was proved by the isolation of the organism in one case and by the epidemiologic, clinical and serologic features of the second. The complete freedom from symptoms until four to five weeks after exposure to *B. suis* makes it unlikely that the illnesses represented a recrudescence of a subclinical infection contracted many years before.

It is unfortunately true that there is no laboratory test by which immunity to brucellosis can be measured.[1] In view of this fact, one can only theorize as to

the importance of the various factors involved in the pathogenesis of these reinfections. One may assume that, as in many other bacterial diseases, the immunity conferred by the first attack is a relative one which may be overcome by a sufficient inoculum. However, infections presented here were the result of exposure to relatively few organisms when compared to the numbers which may be ingested in contaminated milk, or the numbers to which the veterinarian, packing house employee or farmer may be exposed. On this basis, the inference is made that in these two patients the resistance to infection was not significantly increased as a result of their prior subclinical infections.

One can only speculate regarding the importance of the long interval between the primary infection and the reinfection, and the possibility that different species of Brucella were involved.

SUMMARY

Two cases of acute brucellosis which are considered to be examples of reinfection have been presented.

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SALMONELLA SENFTENBERG PNEUMONIA: REPORT OF A CASE*

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SINCE the description of *Salmonella senftenberg* in 1928 by Kauffmann,[1] the organism has been isolated in many outbreaks and has shown the ability to produce a wide variety of clinical manifestations. In 1946, Seligman and his coworkers[2] at the New York Salmonella Center recorded a series of 2,000 human infections, of which two were caused by the senftenberg type; in an earlier series

*Received for publication July 12, 1949.
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of 1,000 cases, the same authors recorded nine senftenberg infections. Rubenstein et al.[3] observed 771 cases of salmonellosis between 1937 and 1945, and found seven due to *S. senftenberg*. Edwards et al.[4] identified 67 various types in a series of 7,318 outbreaks of salmonella infection in man, animals and birds. *S. senftenberg* was the etiologic agent in 12 out of 1,677 outbreaks in man.

As to clinical manifestations, there are three clinical types of salmonellosis. The first, the gastroenteric form, is manifested by diarrhea, fever, abdominal pain, vomiting and headache. The severity varies from a mild, dysenteriform enteritis to a severe cholera-like syndrome. All serologic groups of salmonella may produce this form of infection, but *S. typhimurium* is the most frequent. The second type is salmonella fever, called also typhoid or paratyphoid fever, characterized by fever, malaise, leukopenia and a slow pulse. The temperature elevation may be continuous or spiking, and usually lasts one to three weeks. The most frequently found causative agents are *S. typhi* and *S. paratyphi B*. The third type is the septicemic type, with protean manifestations and high mortality. It is characterized by marked invasiveness, spreading by continuity from an infection in the alimentary tract or through the blood stream. This type tends to localize in the lungs, bones or joints and is most often caused by *S. choleraesuis*. Sachs and Antine [5] reported five cases of salmonella infection using the previously cited classification; one of their cases showed a right lobar pneumonia with *S. choleraesuis* as the causative agent.

Pulmonary lesions due to salmonella have been described by various authors. Edwards et al.[4] reported salmonella from pleural fluid in one case and from empyema in four cases. Bullowa,[6] however, was the first to report a case of pneumonia in which the infecting organism was *S. choleraesuis*. The patient had a right middle lobe pneumonia of which he died after an illness of six days. This was the only case of salmonella infection among 800 consecutive admissions for lobar pneumonia at the Harlem Hospital in New York. Levine and Plattner [7] reported three additional cases of *S. choleraesuis* pneumonia from the Children's Division of the Cook County Hospital in Chicago. Cohen et al.[8] reported a case of *S. choleraesuis* bacteremia with pericarditis, pneumonitis and pleural effusion. In a review of the literature from 1919 to 1935 they found 39 cases of *S. choleraesuis* bacteremia, among which were six cases of pleuropulmonary involvement. D'Albora et al.[9] reported an outbreak of salmonella infection among the personnel and patients of an army general hospital. This outbreak was due to a *S. montevideo* strain. Nineteen cases (6 per cent) had bronchopulmonary involvement. Of these 19 cases, 14 showed roentgen-ray changes typical of interstitial pneumonia, four had acute bronchitis, and one had a frank bronchopneumonia with bloody sputum which contained *S. montevideo*.

The first fatal case of human intestinal infection caused by *S. senftenberg* was reported by Curphey.[10] The organism was isolated during life and at post mortem from a patient with recurrent diarrhea. No pulmonary symptoms were present and on autopsy examination the lungs were normal.

To our knowledge, no previous case of pneumonia due to *Salmonella senftenberg* has been reported.

Case Report

A 42 year old colored female was admitted to the Cook County Hospital in coma on December 5, 1948. The history, obtained from a relative, was that she had been

ill for one week with headache and back pain. She had become progressively more lethargic and lapsed into coma about 12 hours before admission. Past history included a selective dyspepsia for pork and cabbage, a chronic nonproductive cough of 10 years' duration, and two pregnancies, in 1931 and 1934, both ending in miscarriage. She had been previously admitted in April, 1945, for a complaint of hematuria and dysuria, at which time the diagnosis of urethral stricture was made. She was treated

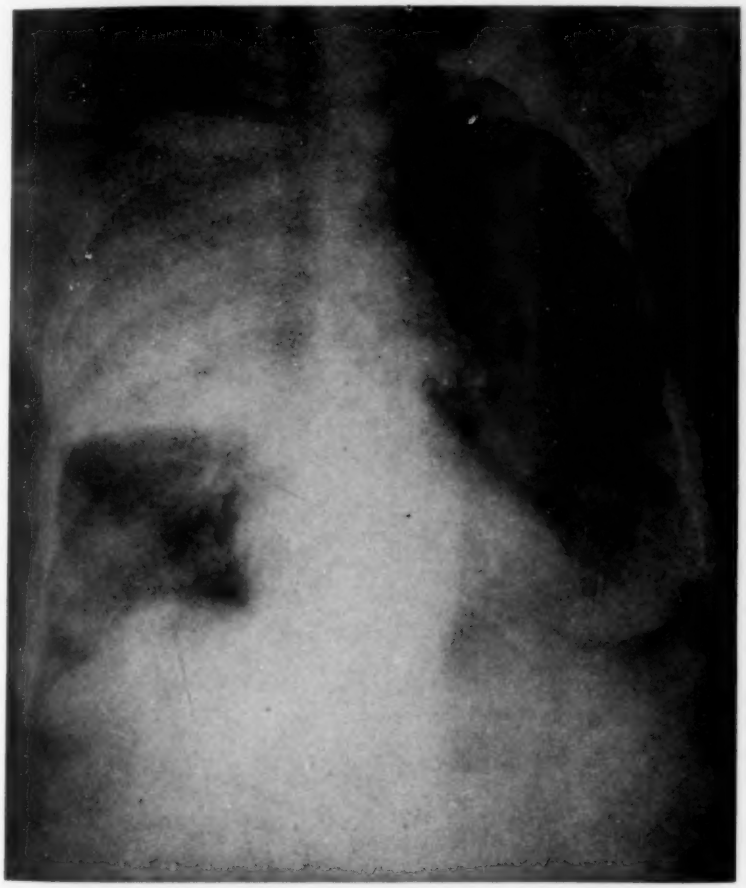

FIG. 1. Showing lobar distribution and complete consolidation.

by urethral dilatations. At that time her non-protein-nitrogen was 26 mg. per 100 c.c. of blood, and the Kahn reaction was 4 plus positive.

Physical examination at the time of the present admission revealed a thin colored female who responded to neither questioning nor stimulation. Temperature was 99° F., pulse 116 per minute, respirations 26 per minute and blood pressure 110 mm. Hg systolic and 70 mm. diastolic. There was marked icterus of the sclerae. The lower lids and the nasolabial folds were covered by pinpoint white crystals which were interpreted as uremic frost. There was moderate nuchal rigidity. The chest was symmetrical, the percussion note was flat in the upper two-thirds of the right

lung posteriorly, and resonance was diminished in the right base. There were showers of inspiratory, crepitant râles in the right apex posteriorly, with bronchial breath sounds. Amphoric breathing was heard in the upper two-thirds of the right lung anteriorly and posteriorly. The heart was of normal size and contour; there was a moderate tachycardia, and a systolic apical murmur was heard. The abdomen was distended and liver dullness was present 4 cm. below the right costal margin,

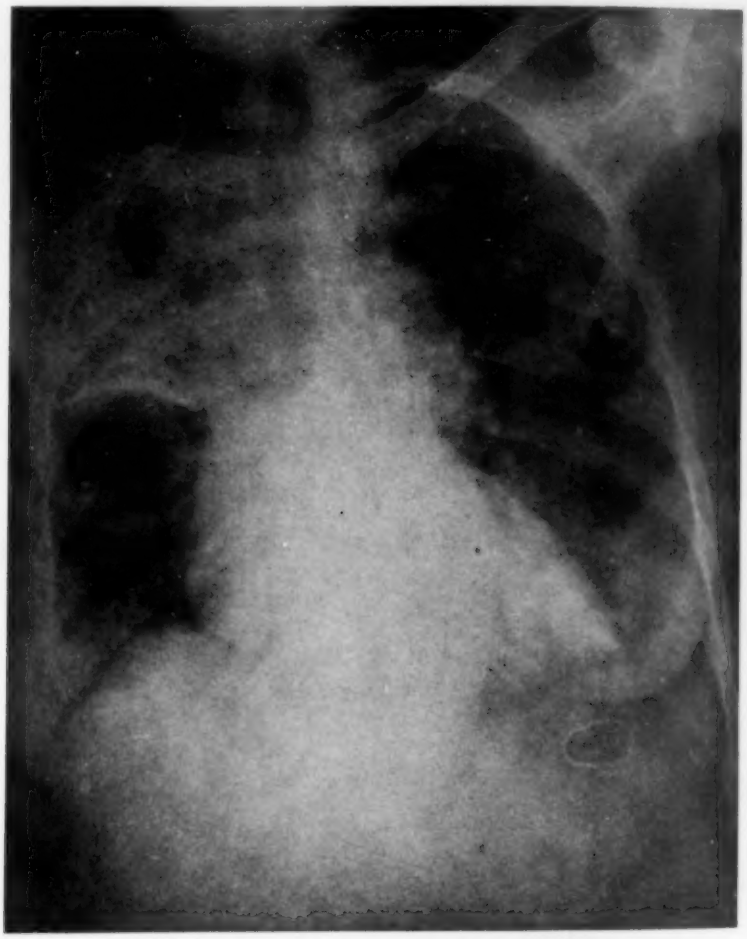

FIG. 2. December 16, 1948, showing resolution.

although the edge was not palpable. Vaginal and rectal examinations were negative. The extremities did not show pathologic changes.

Penicillin, 40,000 units every three hours, was begun the day after admission. In addition, continuous daily infusions of 2,000 c.c. of normal saline and 1,000 c.c. of 5 per cent dextrose in saline were given. Chest roentgenogram taken December 8 showed an opacity of the right upper lobe (figure 1). Temperature remained at

99° F. between December 7 and December 15. On December 13, a diffuse urticarial rash was noted; this was assumed to be due to penicillin. Pyribenzamine, 100 mg. four times daily, was started. By December 15 the patient began to respond slightly. Between that date and December 17 her temperature rose to 101.2° F. From then on the temperature remained at normal levels. On December 20, coincident with a marked fall in the non-protein-nitrogen (from 254 mg. per 100 c.c. of blood on De-

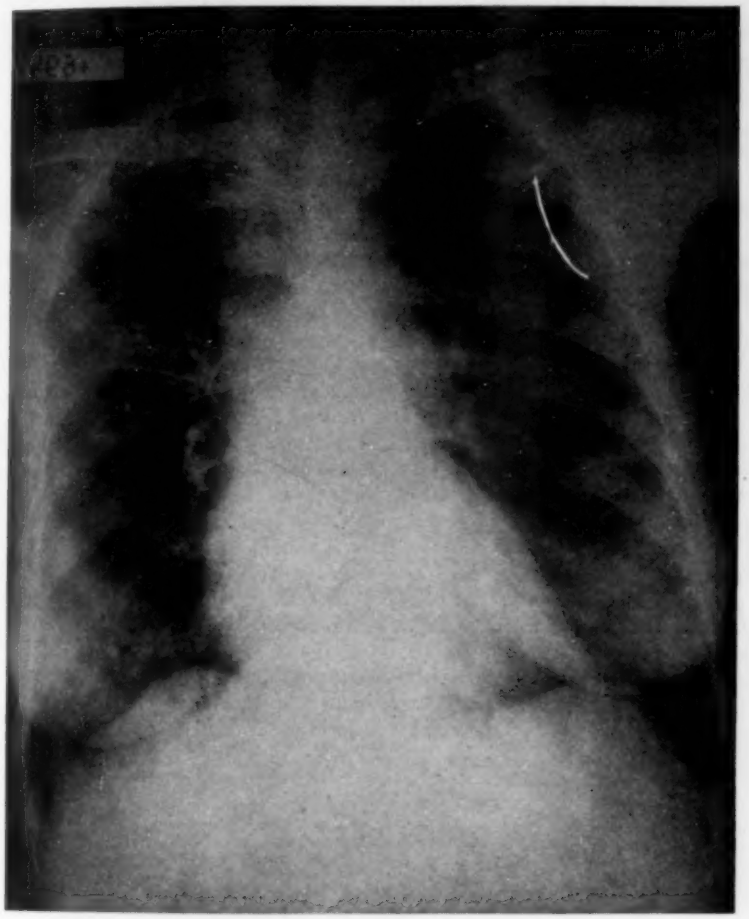

FIG. 3. January 26, 1949, showing complete resolution.

cember 10 to 64 mg. per 100 c.c. of blood), she began to respond well and was able to take fluids and food orally.

Streptomycin, 0.5 gm. twice daily, was begun on December 20. Because of the development of a moderate anemia, the patient received 2,500 c.c. of blood in biweekly transfusions of 500 c.c., beginning December 23. Although clinically recovered by January 6, 1949, she was kept in the hospital for further evaluation of her renal

function. On January 26 the chest was completely clear roentgenologically (figure 3) and she was discharged from the hospital.

Laboratory Data: Urinalysis on admission showed a specific gravity of 1.003, 1 plus albumin reaction, no sugar and 2 plus reaction for bile, no urobilinogen. Repeated urine examinations during the remainder of the hospitalization revealed gradual diminution in the albumin and bile content to negative values, but the specific gravity never rose higher than 1.008.

Lumbar puncture performed shortly after admission revealed a xanthochromic fluid which showed a 1 plus Pandy reaction. Spinal fluid glucose was 76 mg. per 100 c.c., protein was 80 mg. per 100 c.c. and chlorides were 115.4 mg. per 100 c.c. Culture of the spinal fluid was negative for any organism, as was a smear for acid-fast bacilli. The spinal serologic test for syphilis was negative.

Blood count on December 6 showed hemoglobin 71 per cent, red cells 4,320,000 and leukocytes 40,000, with a differential of 97 per cent polymorphonuclear leukocytes, 2 per cent monocytes and 1 per cent lymphocytes. White cell count on December 17 was 33,000. On December 23 the red cells numbered 2,840,000 and the leukocytes 6,000; the smear showed macrocytosis and hypochromia, but no sickling. Blood count on January 12, 1949, revealed hemoglobin 45 per cent, red cells 2,700,000 and leukocytes 10,600, with a differential count of 69 per cent polymorphonuclear leukocytes, 5 per cent eosinophils, 3 per cent basophils, 17 per cent lymphocytes and 6 per cent monocytes.

Sputum culture on December 14 showed *E. coli, A. aerogenes,* paracolon organisms, *Salmonella senftenberg,* beta hemolytic streptococci and *M. catarrhalis.* The sputum was reëxamined two days later and showed *E. coli* and *S. senftenberg.* Sensitivity studies showed the salmonella to be extremely resistant to penicillin (more than 300 units) and highly resistant to streptomycin (more than 40 micrograms). Blood culture drawn December 14 had no growth at the end of two weeks. A stool culture was reported on January 3 to be positive for *S. senftenberg.* Blood agglutinations were reported on January 3 to show Typhoid H, 1:80, Typhoid O, 1:80, salmonella polyvalent antigen positive, and *S. senftenberg* (own strain) 1:360. Urine culture on the same date did not show pathogenic microörganisms. Sputum examinations for tubercle bacilli were negative on December 14 and 16, as were gastric washings on January 13 and 15.

The blood Kahn test on December 14 was doubtful; when repeated, the Kahn was again doubtful, but a positive Wassermann was obtained.

Blood chemical examinations were as follows:

Date	12-7	12-10	12-14	12-16	12-20	12-29	1-6
Non-protein-nitrogen	162	254	196	126	64	34	30
Creatinine	6.6	8.0	5.6	4.2	3		1
Inorganic phosphorus	7.5		9.2		6.9	5	
Chlorides	95.7				107.7		102.5
Sodium					140.8	137	
CO_2 combining power	42						49.5
Icterus index	104	55	8		11	6	
Cephalin flocculation	2 plus		1 plus		2 plus	3 plus	
Thymol turbidity	11.6		14.4		12	7	
Total proteins			8		7.3	7.8	
Albumin					3.4	3.1	
Globulin					3.9	4.7	
Cholesterol			150		108	135	
Alkaline phosphatase	6.3		21.2		10	10.2	

Renal function studies were as follows:

Date	Normal Values	1–6	1–24	3–4	4–20
Urea clearance	75 c.c. per min.	35.5	29.5	41.8	51.5
Creatinine clearance	120–150 c.c. per min.	51	50	66.6	57.5
Mannitol clearance	125 c.c. per min.	45.3	39.1	52.1	64.9
Paha clearance	600 c.c. per min.	235.8	220	323.5	282
T_m	90 mg. per min.	23.5	34.1	48.8	36.9
Filtration fraction	.20	.19	.17	.16	.23
C_{paha}/Tm_{paha}	7.6	10	6.98	6.68	7.64

Discussion

We have presented a case of pneumonia in which the etiologic agent was *S. senftenberg*. Clinical and roentgenologic findings unquestionably established the diagnosis of a lobar pneumonia, but not until sputum examinations showed the presence of *S. senftenberg* was our attention directed toward this unusual causative agent. Of interest was the presence of a previously damaged kidney, which, with the additional strain of a severe infection, gave rise to a marked nitrogenous retention and the subsequent abnormal clearances. Clinical and laboratory findings also pointed to the development of a hepatitis. A good therapeutic response was obtained with general supportive measures, despite the marked resistance of the organism to both penicillin and streptomycin.

Summary

The literature on salmonella pneumonia has been reviewed. A case of pneumonia has been described from which sputum and stool cultures of *S. senftenberg* were recovered and in which agglutinations with *S. senftenberg* were positive. It is believed that this is the first reported case of pneumonia due to *S. senftenberg*.

Acknowledgment

The authors wish to thank Dr. Oscar Felsenfeld and the Department of Bacteriology, and Dr. William S. Hoffman and the Department of Biochemistry, Cook County Hospital, for their assistance.

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DISSECTING ANEURYSM OF THE AORTA: TWO CASES WITH UNUSUAL ONSETS *

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Much interest has developed in the diagnosis of dissecting aortic aneurysm. Although up to about a decade ago this vascular disease was merely a postmortem surprise, now it is frequently recognized clinically. Physicians are rapidly becoming more aware of the possibility of a dissecting aneurysm when considering the differential diagnosis of sudden severe pain in the chest, especially in hypertensive patients.

Pathology

Changes in the medial layer of the aorta are usually found. The nature of these changes may be different in various cases, but they are important for the formation of the dissection. The typical medionecrosis of Erdheim [1] is not found in all cases.[2] In patients under 40 years of age there seems to be some relationship between pregnancy, coarctation of the aorta and dissecting aneurysm.[3] In the latter circumstance, whether hormonal influence or disturbed lipoid metabolism or both play a rôle is not known. An intimal tear is not always present.[4, 5, 24] Whether this rent is primary or secondary to the medial changes is not agreed upon at present. This controversy will be discussed later. Intimal tears without dissection have been reported and labeled as "incomplete rupture of the aorta." [6]

Intimal tears may occur at any point along the aorta but are more often found in the ascending aorta near the aortic ring, and frequently in that portion of the wall which is within the reflected pericardial sac.

The dissection may take one of three courses: (1) progress and involve the entire aorta and then rupture back into the lumen; (2) progress for a variable distance along the aorta and stop, or (3) rupture through the adventitia into the pericardial, pleural or abdominal cavities. The last event is the most common, occurring in 80 to 90 per cent, with sudden death.

Clinical Picture

Although the clinical picture of dissecting aortic aneurysm is variable, there are certain features which can be considered definite clinical manifestations of a

* Received for publication June 2, 1949.
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typical case. The most striking feature attending the onset of the splitting of the aortic wall is severe pain. It is usually excruciating and extensive, radiating from midthorax, front or back, through the chest, down the back, up to the neck, or even to the thighs and legs, and only rarely to the arms. The pain comes suddenly at its maximum, often is prostrating and induces a state of shock or death.[7] The pain may start in the upper abdomen, the lumbar region, the interscapular region, or rarely in the legs, radiating into the abdomen or thorax. Very rarely the pain may originate in the episternal notch [5, 8] and radiate to the epigastrium, as in case 2, reported below. However, pain may be altogether absent.[5] It may be so mild, transient and late in appearing as either to escape notice or to have its meaning misunderstood. The first case reported below is an example of this.

Another important symptom or group of symptoms is dependent on the blocking of the vessels involved. Thus, pain, numbness, weakness of an extremity, syncope and bizarre neurologic signs may arise.[7, 9] Renal pain and hematoma of a renal artery resulting from splitting of the aortic wall have been described.[10] Hematuria and hematoma of a renal artery were present in the second case reported.

Dyspnea is usually not marked or frequent and, when present, is secondary to pain. When dyspnea occurs hours or days after the onset, hemothorax resulting from a leaking dissecting aneurysm should be considered.[11]

Syncope is not infrequently seen and usually follows the pain.[5] Since as a rule the blood pressure does not fall, the syncope is probably due to interference with the circulation to the brain as a result of the dissection. However, carotid sinus stimulation may play a part in the causation of syncope.

The relationship of trauma, undue exertion and excitement to the formation of dissecting aneurysm is still disputed. In most cases, however, such predisposing factors are still elicited.

Hypertension is frequently present. Although it was formerly believed that it was of prime importance to the formation of a dissecting aneurysm,[4] recent investigators maintain that hypertension is of secondary importance.[12, 13] Hypertension is seen in 70 to 80 per cent of cases over the age of 40, and in 40 to 50 per cent of patients under 40 years of age.[8] Hence, the absence of hypertension does not rule out a dissecting aneurysm. It is doubtful if an increase in the blood pressure alone could reach sufficient magnitude in the human subject to cause an aortic dissection, according to Sailer.[2] Nevertheless, it would seem possible in the presence of a diseased media and secondarily involved intima. Unlike most of the cases of coronary occlusion, the blood pressure in dissecting aneurysm usually maintains its original level.

Only rarely do blurring of vision and headache usher in dissecting aneurysm, as in case 1 below. Cases with blurring of vision associated with constricting chest pain have been reported.[14]

A diastolic murmur over the precordium, heard best at the aortic area, is a frequent and important diagnostic finding when it appears following the onset of the dissection.[15] It is due to the sagging of the aortic commissural attachments, as a result of the intimal tear. This murmur may, at times, be musical or squeaky. Such was the quality of the murmur in our second case. A systolic

murmur usually accompanies it. This is not of much diagnostic significance, since these patients are likely to have such a murmur before the dissection sets in.

A pericardial friction rub is not a frequent finding, but occasionally it occurs hours or days after the onset.[16] This is due to a small leakage of blood into the pericardial cavity, which sets up a fibrinous pericarditis. When not properly interpreted, this rub will lead to a misdiagnosis. Such was the situation in case 1 reported below. However, a pericardial friction rub in dissecting aneurysm of the aorta may be due to the chronic nephritis that some of these hypertensive patients may have.[17]

Ecchymosis of the abdominal wall, taking the form of a purplish discoloration of the skin of the left lower quadrant, has recently been described as an early sign. This is due to bleeding from the left deep inferior epigastric artery.[18]

A double thrust in the neck on the side into which the dissection extends, as compared with a single thrust on the normal side, has been recently described.[19] This double thrust is due to the pulsation in the main lumen and the acquired one of the vessel involved.

A pulsating tumor may occasionally be seen in the inguinal region, or pulsation may be felt on either side of the spinal column, as the dissection proceeds down the aorta. Such a swelling in the inguinal region may be mistaken for an abscess, with disastrous results.[20]

A systolic thrill may at times be elicited over a peripheral vessel if the dissection extends into it. A thrill was elicited over the right carotid in a case reported by Kinney et al.[3] In our second case there was a thrill in the episternal notch, probably caused by direct transmission from the site of the tear, which was not very far down.

There may be a moderate leukocytosis with increase in the polymorphonuclears and not infrequently the blood sedimentation rate is increased. A progressive anemia as a result of bleeding within the aortic wall has been reported.[17] The serologic reaction for syphilis in the blood is usually negative.

Roentgenologic examination may at times be of aid. There may be an increase or deformity in the supracardiac shadow, or an arcuate excrescence extending outward from some point in the aortic arch, which may pulsate. Changes in the aortic width in successive films are pathognomonic. There is usually cardiac enlargement.[21]

The electrocardiogram is not pathognomonic. When the dissection involves a coronary artery, a tracing characteristic of myocardial infarction is obtained,[22] or when leakage into the pericardium occurs, this may suggest pericarditis, as reported by Sacks[16] and as seen in our first case. Various arrhythmias may be seen rarely, depending upon the extension of this hematoma into the various parts of the conduction system. Left heart strain is seen when hypertension is present.[5]

Differential Diagnosis

It may be differentiated from coronary occlusion by the severity of the pain, which radiates widely, by syncope, maintenance of the blood pressure level, the sudden appearance of a diastolic murmur, early blockage of peripheral arteries, absence of positive electrocardiographic findings, even when the tracing is taken as late as a week or so after the onset, and, at times, by roentgenologic evidence

of deformity of the aortic arch. However, the differentiation frequently cannot be made.

It has been mistaken for syphilitic aortitis, cerebrovascular accident, mediastinal tumor, pneumonia, diaphragmatic hernia, pancreatitis, cholelithiasis, nephrolithiasis, ruptured peptic ulcer, embolic occlusions, mesenteric thrombosis and diseases of the spinal cord.

Course

Only 10 to 20 per cent recover from the first attack, but half of these develop a second fatal attack months or even years later [5]; the rest recover and die from some other disease or accident.[5, 23]

The following two cases are reported because of their unusual onsets. In the first, pain did not play a major rôle in the symptoms but evidences of pericarditis were the outstanding features. In the second, while pain was excruciating, its location was unusual, in the episternal notch. Pathologically, the first case was of much interest, since there was no evidence of an intimal rent in the aorta.

Case Reports

Case 1. A 43 year old married surgeon was admitted to the Mount Sinai Hospital, service of Dr. Harry J. Isaacs, on February 4, 1945, because of blurring of vision, severe frontal headache, nausea and weakness of one hour's duration. He had had moderate hypertension for a number of years but without any symptoms. He considered himself well and was actively engaged in the practice of surgery. The symptoms mentioned above began while he was driving to the hospital on a very slippery and icy boulevard. He reached the hospital, rested for a few minutes and proceeded with his daily rounds. However, because of his marked pallor and apparent weakness, the author, who happened to be on the same floor at the time, persuaded him to be admitted to the medical ward. He denied having any pain in the chest, complaining chiefly of headache and some blurring of vision.

Physical examination revealed a sallow complexion in contrast to his usual florid one. The patient showed slight apprehension but was otherwise comfortable. Temperature was 98° F., pulse 82, regular, and blood pressure 145 mm. Hg systolic and 100 mm. diastolic. The pupils reacted to light and accommodation, and ocular movements were normal. There was no abnormal arterial pulsation of vessels of the neck. Funduscopic examination revealed grade III arteriosclerosis. There was no cervical rigidity. There was no adenopathy. The lungs revealed no abnormality. The heart measured 3.5 by 13.5 cm. There was no appreciable supracardiac dullness. No thrills were felt. A short systolic murmur was elicited at the apex, and the aortic second sound was accentuated. The abdomen was not abnormal. The femoral arteries pulsated normally. The reflexes were normal. The urine was negative, and the admission blood count was within normal limits. The patient was given a sedative.

In the evening of admission, about 10 to 12 hours after the onset of symptoms, he first noticed mild to moderate interscapular pain, radiating to the hips. This was transient, requiring no narcotic, and the patient spent a comfortable night. On the following morning he decided, against the advice of his physician, to go down to the operating room to carry out a previously scheduled operation. However, he soon had to give up the effort because of nausea, headache and weakness. He was put to bed, and several hours later he began experiencing sharp pains in the center of his chest, greatly aggravated by merely talking or breathing deeply. Examination at this

time revealed a temperature of 98° F.; respirations were 24 and regular. The lungs were clear, the pulse was 84 and regular, and cardiac findings were as previously found. No thrill or adventitious sound was heard. The blood pressure was 150 mm. Hg systolic and 100 mm. diastolic. The electrocardiogram revealed left axis shift, T_1 slightly lower than T_3 (figure 1). Codeine was given.

On the next day he felt somewhat better but still complained of the same precordial soreness upon talking or breathing deeply. There was no change in pulse

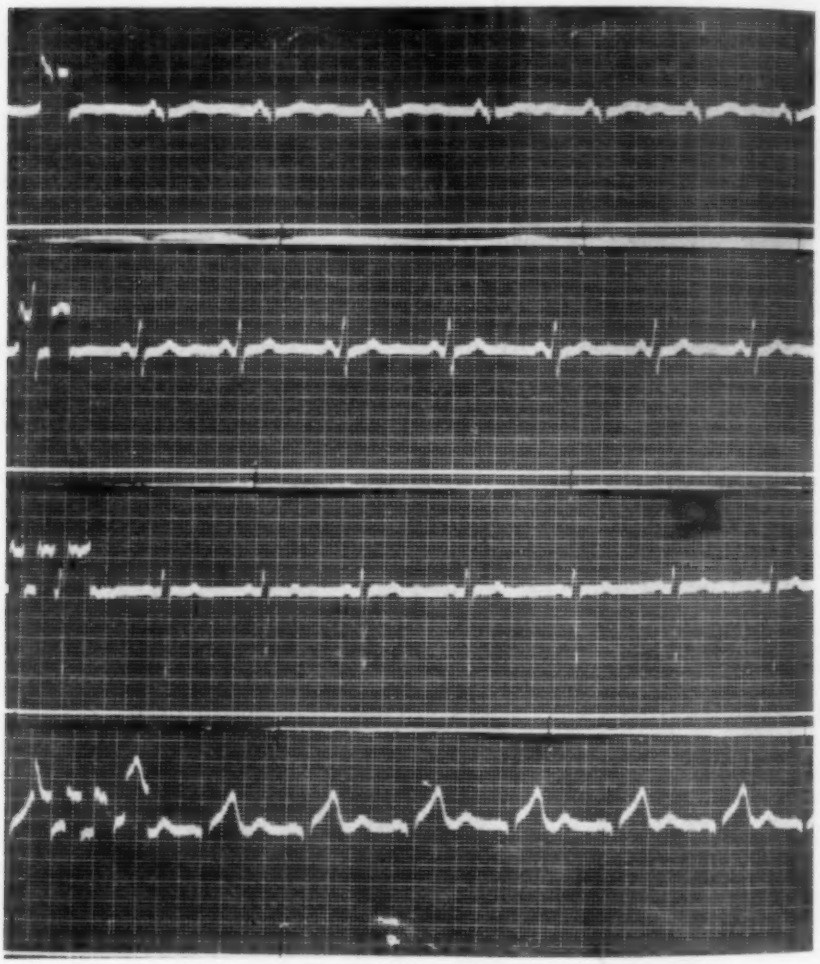

FIG. 1. Left axis shift. T_1 slightly lower than T_3.

or blood pressure, but a definite pericardial friction rub was elicited, best heard at the level of the second and third left interspaces. The blood sedimentation rate was 43 mm./per hour against the normal of 20 mm. The blood count showed hemoglobin 90 per cent; red blood cells 4,810,000; white blood cells, 11,700, polymorphonuclears, 85 per cent. The serological reaction for syphilis in the blood was negative. The electrocardiogram at this time revealed ST_3 and ST_4 slightly elevated (figure 2).

The roentgenogram by Dr. J. Arendt revealed enlargement of the left ventricle and prominence of the vascular pedicle on the right with a straight line going upwards, indicating stasis of the vena cava. Two days later (February 8), the electrocardiogram showed definite elevation of ST_1 and slight elevation of ST_2. T_1 and T_3 were inverted. ST_3 was depressed and T_3 was diphasic. Lead IV showed no abnormalities (figure 3). At this time a diagnosis of pericarditis with possibly some degree of left

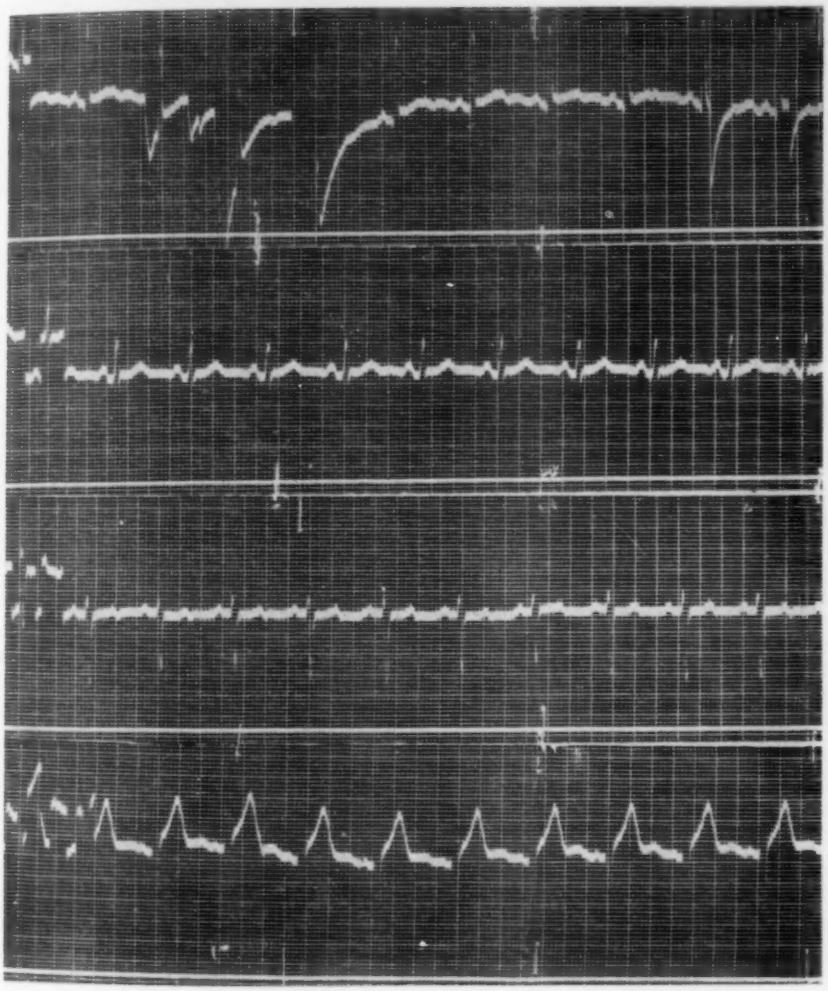

FIG. 2. Left axis shift. ST_1 and ST_4 slightly elevated.

heart strain was made. On this day the patient felt so well that he insisted, against the advice of his physician, upon getting out of bed and walking around in his room.

On February 10 the patient denied having any discomfort and planned to leave the hospital in a day or so. The friction rub was still present and the blood pressure and pulse were about the same. He looked and acted like one on the way to recovery. That same day, while having his evening meal, he suddenly collapsed and died.

Autopsy (by Dr. I. Davidsohn):

Cause of Death. Ruptured dissecting aneurysm of the ascending aorta, arteriosclerosis, grade 3, hemopericardium, acute fibrinous pericarditis, eccentric hypertrophy of the heart, coronary sclerosis, grade 3, acute passive congestion of the liver, spleen and kidneys.

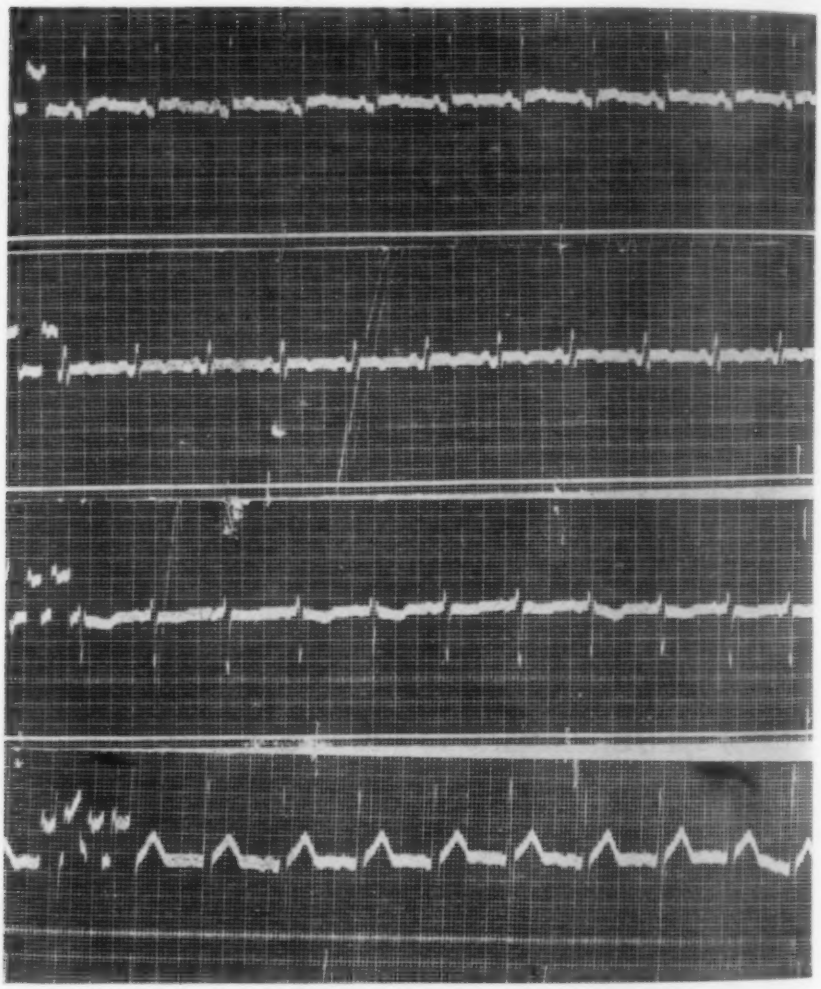

FIG. 3. Left axis shift. ST_1 elevated and T_1 terminally inverted. ST_2 slightly elevated and T_2 inverted. ST_3 depressed and T_3 diphasic to inverted.

Histologic Diagnosis. Medionecrosis cystica: arteriosclerosis and coronary sclerosis.

Autopsy Findings. The pericardial sac was completely filled with 350 c.c. of clotted and liquid blood. The main coronary branches showed marked sclerosis and calcification of the anterior left descending branch but without narrowing of the lumen. There was no evidence of myocardial infarction.

Aorta. The ascending part of the aorta, just above the aortic orifice and within the pericardial sac, showed anteriorly and to the right a hematoma in the wall, bulging anteriorly and measuring 7 by 6 by 4 cm. (figure 4). The intima in this area was thinned out and purplish in color because the hematoma showed through it. The adventitia showed a tear, about 5 mm. long and 1 to 2 mm. wide, through which

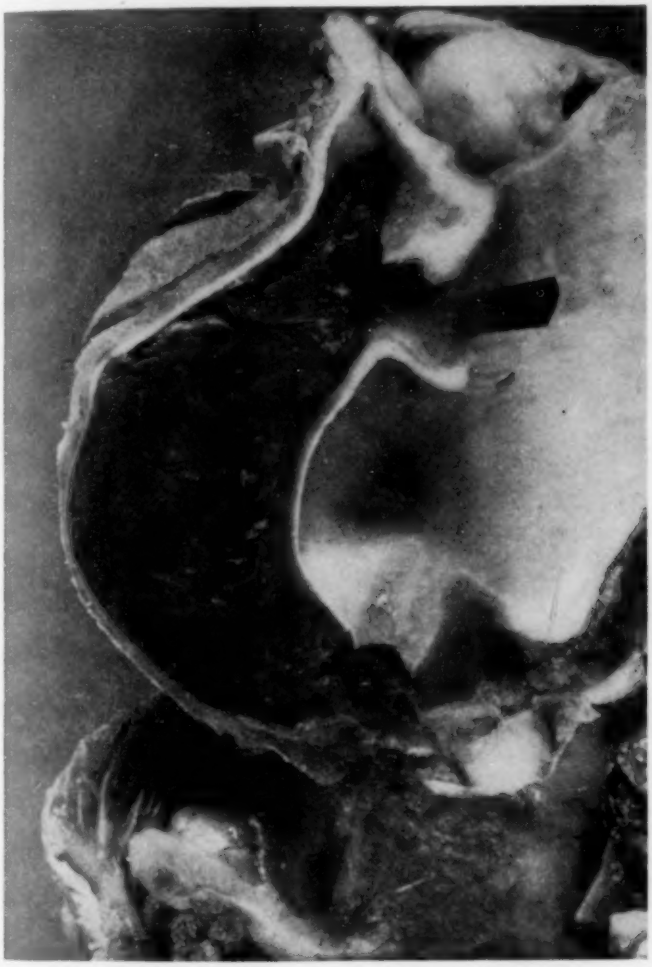

FIG. 4. Hematoma in the wall of the aorta. Arrow indicates place where a section of the bulging intima was removed for study; hence, the discontinuity.

hemorrhage into the pericardial sac occurred. The hemorrhage was between the intima and the adventitia. No defect in the intima which might have served as a source of the hematoma could be seen. The remaining aorta, especially the abdominal portion, showed marked arteriosclerosis. Three centimeters above the aortic valve the aorta measured 8 cm. in circumference, the ascending portion above it measured 5.8 cm., the descending, 5.8 cm., and the abdominal portion, 4.8 cm.

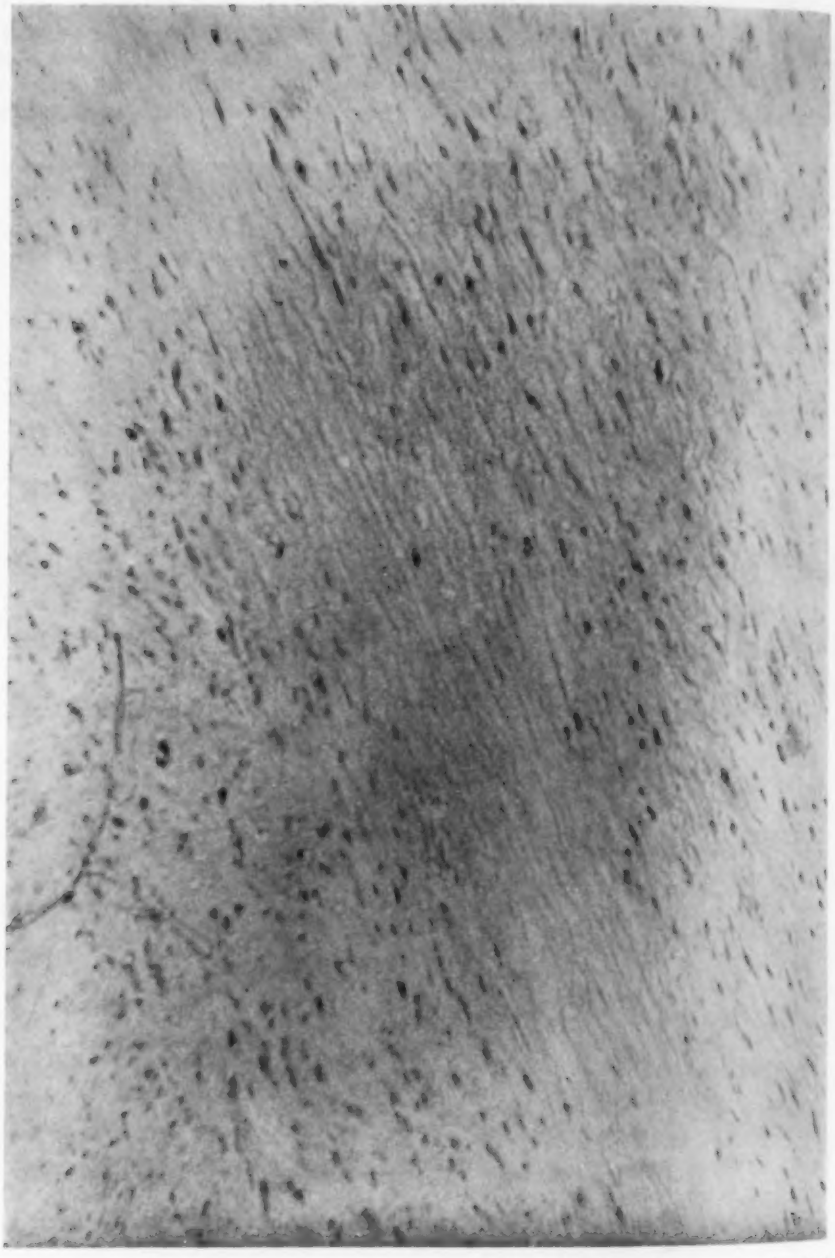

FIG. 5. Section from the region of the dissection, showing diffuse necrosis of the several layers of the media in the form of cellular necrotic tissue, separating the preserved outer and inner layers.

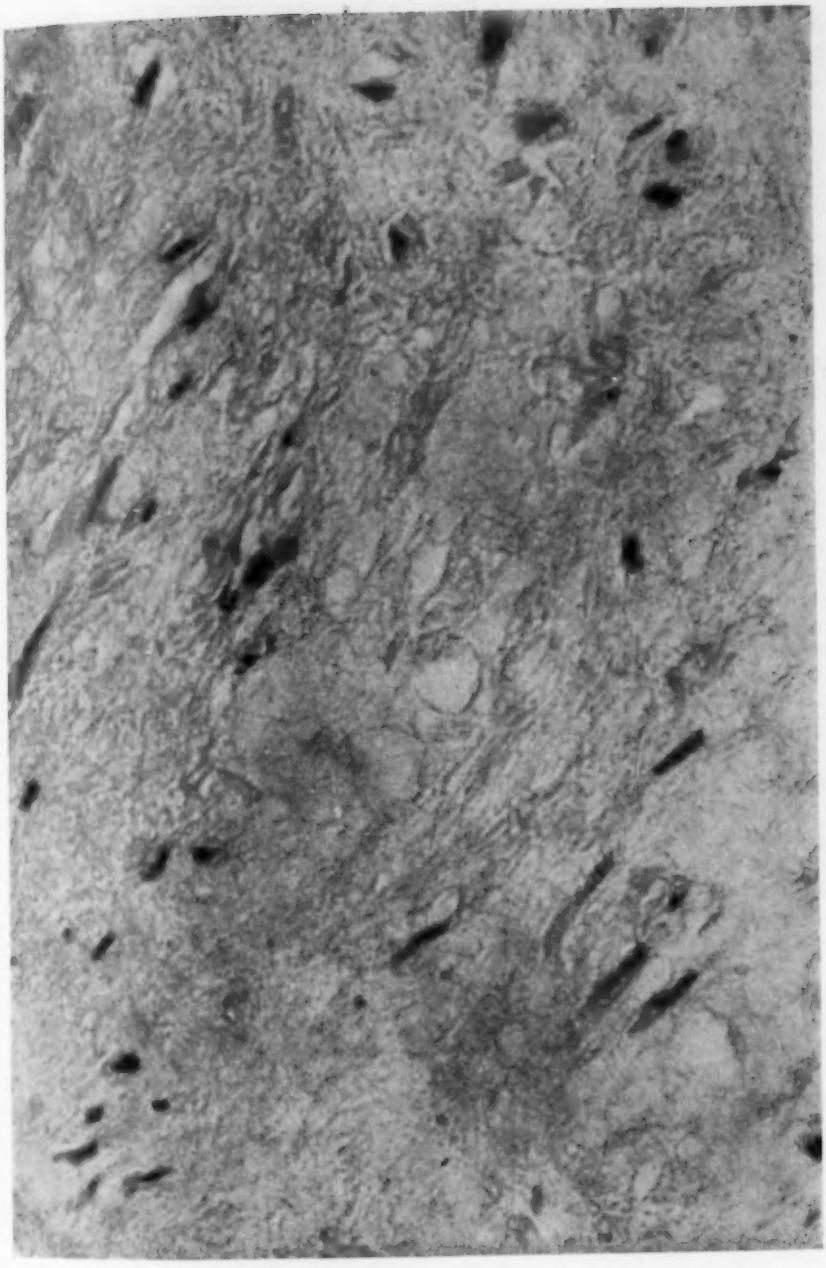

FIG. 6. Root of aorta, showing early necrotic changes in muscularis.

Microscopic Study. Sections from the ascending portion in the region of the dissection showed diffuse necrosis of the several layers of the media, in the form of cellular necrotic pink-staining tissue, separating the preserved outer and inner layers of the media very clearly. There were also small cystic areas with similar breakdown and necrosis. These changes extended down to the area of the actual hemorrhages, at both the proximal and the distal ends. The intima in the thinned-out portion in the region of the aneurysm also showed necrosis and infiltration with neutrophilic leukocytes. It had the appearance of being on the verge of breaking through. In the outer layer of the aneurysmal sac there were also areas of necrosis and diffuse proliferating granulation tissue extending into the subepicardial area (figures 5 and 6). The heart muscle fibers showed diffuse hypertrophy and an increase in the connective tissue. The kidneys, spleen, pancreas and adrenals showed marked arteriosclerosis.

Case 2. A 49 year old married male negro cook was admitted to the Cook County Hospital on September 30, 1945, because of sudden, sharp pain in the throat, radiating substernally into the abdomen and both arms, of several hours' duration.

Onset. The patient had considered himself well until several hours before admission when, while playing cards with friends, he developed the symptoms mentioned above. The pain was severe and constant, mainly in the episternal notch, and was aggravated by talking, breathing or movement of the body. The pain was not referred to the back or the lower extremities. After vomiting once he experienced some relief. His previous history revealed no serious illness or venereal infection and his family history was not contributory. His habits were not unusual.

Physical examination revealed an acutely ill man, tossing around in bed because of excruciating pain and having difficulty in breathing and talking. Temperature was 98° F.; pulse 78, regular and equal in both radials; blood pressure 165 mm. Hg systolic and 60 mm. diastolic; respirations regular. The eyes were not abnormal. The pupils reacted normally. The neck veins were not distended. There was visible pulsation in the vessels of the neck and in the episternal notch. Here a systolic thrill was palpable and definite tenderness was elicited. The heart measured 3 by 10.5 cm., with no widening of the supracardiac area. No precordial thrill was elicited. There was a fairly rough systolic and an early diastolic murmur at the apex, pulmonary and aortic areas. In the latter areas, the diastolic murmur was squeaking in character. The lungs showed a few râles in both bases. The liver was not felt. The femoral pulses were normal and equal. The reflexes were normal.

Laboratory Findings. Urine: albumin 2 plus; sugar, negative. Microscopic examination revealed a moderate number of red blood cells. The blood showed a hemoglobin of 87 per cent; red blood cells 4,900,000, white blood cells 7,000, and 83 per cent polymorphonuclears. The roentgenogram showed the cardiothoracic ratio to be slightly increased. The electrocardiogram revealed low voltage of the QRS complexes. T_1 was low, T_4 was terminally inverted. The diagnosis of dissecting aneurysm of the aorta was made. Syphilitic aortitis with insufficiency and aortic rupture was considered as the next possibility.

Course. When seen on the second day after admission, the patient was asymptomatic. The cardiac findings were the same, and there was no evidence of blocking of any peripheral vessel. He did well until October 4, five days after entrance, when he again developed pain in the episternal notch, radiating to the epigastric area, and died a few minutes later.

Autopsy: Anatomic Diagnosis. Dissecting aneurysm of ascending aorta. Medionecrosis of the aorta. Hemopericardium, 800 c.c. Partial separation of the adventitia from the muscular layer along the entire aorta, with rupture into the lumen of both common iliac arteries. Hematoma of the wall of the left renal artery, arising from the dissecting aneurysm. Left renal infarct. Moderate sclerosis of the aorta

and peripheral arteries. Some eccentric hypertrophy of both ventricles. Acute congestion of the viscera.

The Aorta. Two centimeters above the aortic ring there was a transverse tear in the posterior wall of the aorta measuring 4 to 5 cm. The adventitia was separated from the media, forming an aneurysmal sac which was filled with clotted blood. At one point there was a small perforation of the adventitia leading to a hemopericardium. The aneurysmal sac found a continuation along the entire aorta. Two centimeters below the bifurcation, two transverse tears were seen in each of the common iliac arteries; thus the aneurysm emptied itself back into the arterial lumen. The left renal artery showed a hematoma in its posterior wall, a continuation of the hematoma in the aorta. While the aorta showed some arteriosclerosis in the ascending and descending parts, the area of the tear showed no sclerotic plaques.

Microscopic Examination. Degenerative changes, most marked in the media, involving smooth muscle fibers, collagen bundles and elastic tissue fibers were seen. There were larger confluent cystic areas in many places. The smooth muscle showed changes varying from cloudy swelling to complete degeneration, with disintegration and replacement of the muscle fibers by mucinoid material. The intima showed necrosis and infiltration with leukocytes in the region of the tear. Away from this region, the intima showed no necrosis but some leukocytic infiltration. The adventitia was not remarkable. The vasa vasorum were not unusual. There was no evidence of syphilis.

Comment

The etiology and pathogenesis of dissection of the aorta are not definitely established. Neither is there agreement among the various students of this disease as to the relation of the medial necrosis to the intimal tear, nor as to whether the latter is needed for the production of the aortic split.

According to Blain,[24] there are three opinions concerning the pathogenesis of dissecting aneurysm. According to the first, the intimal rupture is the primary event in the development of the lesion. According to the second, Erdheim's idiopathic cystic medial necrosis, or a similar type of lesion, is the underlying cause for the dissection, but an intimal tear produced by the intraaortic pressure must develop for the aortic blood to enter the weakened media and dissect it. The third view holds that intramedial bleeding due to ruptured vasa vasorum, superimposed on medial degeneration, is the important process. It further holds that the intimal rupture is only a secondary development or, indeed, not even a necessary finding.

Our first case did not demonstrate an intimal tear. Tyson [25] reported five cases, in three of which there was no intimal tear. He also cited a case reported by Krukenberg of a dissecting aneurysm of an inferior thyroid artery without intimal tear. He believes that, in those cases in which the intima is not ruptured, the bleeding must come from ruptured vasa vasorum. When the intimal rent does occur, it is secondary. Mote and Carr [13] reported four cases of dissecting aneurysm without intimal tear. Blain [26] reported a case without an intimal rent, and collected 15 such cases from the literature.

Hence, it is quite clear that some dissecting aneurysms occur in the absence of an intimal rupture. Whether the intimal tear observed in most of the dissecting aneurysms is secondary to the medial hemorrhage is not known, but it is possible. The fact that cases of dissecting aneurysms occur without rupture of the intima suggests strongly that the source of the blood in the medial tear is dam-

aged vasa vasorum. This may hold for all dissecting aneurysms, whether the intima is intact or not.[24] However, in our case with the intimal tear, the vasa vasorum were not unusual.

Case 1 had marked arteriosclerosis and arteriolosclerosis of various organs and yet no intimal tear was present. Case 2, on the other hand, had only moderate sclerosis of the aorta and peripheral vessels and no evidence of arteriolosclerosis, but an intimal rent was demonstrated. Moreover, in the area of the intimal rupture no sclerotic plaques were found. This observation suggests that, if arteriosclerosis plays a rôle in the pathogenesis of arterial dissection, it is probably only contributory in nature.

Weiss [22] and Sailer [2] point out that syphilis plays no rôle in etiology. The pathologic process in this disease tends to fuse the various layers, thus hindering dissection.

The clinical onset of our first case was bizarre, since blurring of vision, headache, nausea and weakness, and not pain, were the presenting complaints. Some mild and transient pain in the interscapular area radiating to the hips was experienced 10 to 12 hours after the onset. When soreness in the anterior chest appeared together with the pericardial friction rub, pericarditis was the logical diagnosis. The increased blood sedimentation rate was interpreted as evidence of some infectious process.

Evidence of pericarditis occurred on the second day of his illness, five days before death, which means that a small perforation into the pericardium took place that allowed a small amount of blood to escape, enough to cause a fibrinous pericarditis but too little for the production of a cardiac tamponade. The fact that the patient lived for five days without any cardiac embarrassment or evidence of a gradually increasing cardiac compression speaks for the minuteness of the rupture and for its probably being sealed off by fibrin. When the perforation increased, a fatal cardiac tamponade ensued. That there may be a dissecting aneurysm slowly leaking into the pericardial cavity, causing a cardiac tamponade lasting for a number of days and exhibiting all the classical signs of cardiac compression, was illustrated by a recently reported case.[27] Both of our cases show that rupture of a dissecting aneurysm into the pericardial cavity is not necessarily immediately fatal.

Although the second case had the typical onset of excruciating pain, its localization in the episternal notch was rather unusual and its radiation to the arms was also uncommon. Since the autopsy did not demonstrate the dissection compromising a coronary artery, it is possible that the sudden onset of the aortic insufficiency produced a relative coronary insufficiency with resulting pain in the arms. Considering the extensive dissection in this case, ending in both common iliac arteries and involving one renal artery, one is surprised at the absence of pain either in the back or in the lower extremities.

The diastolic murmur and the thrill have already been discussed. These two findings were of aid in making an antemortem diagnosis. Although it is only of academic interest, the presence of these findings should predict an intimal tear of the ascending aorta in a clinical case.

Why this patient had an intimal rent, and the first case, with so much more vascular disease did not, is difficult to explain. It certainly could not be ascribed

to the somewhat higher systolic pressure in this case—165/60 against 145 in the first. For the present, it has to be considered as merely fortuitous.

However, once an intimal rupture occurs, more extensive splitting of the aortic layers usually takes place than in the aortae where the intima is intact. The reason for it is no doubt mechanical dissecting force of the inrushing blood with each systole. This is well exemplified in the two cases reported. In the first case, the dissection involved only that part of the aorta which was within the pericardial sac. In the second case, the entire aorta was dissected down both common iliac arteries, where 2 cm. below the bifurcation two transverse tears were seen, the aneurysm thus emptying itself back into the arterial lumen. The result was the so-called "double-barreled aorta."

Finally, in this case as in the first, the aneurysm ruptured into the pericardial cavity but, unlike that in the first case, the rent was larger from the start and the patient died promptly from a massive cardiac tamponade.

Conclusions

Two cases of dissecting aneurysm of the aorta are presented.

The onset in the first was atypical, since pain did not play a major rôle. Blurring of vision and headache were the presenting complaints. Signs and symptoms of pericarditis were the outstanding features from the second day to the seventh, the day of sudden death from cardiac tamponade. The clinical diagnosis was pericarditis.

The second case began with pain, but situated primarily in the episternal notch, where severe tenderness and a systolic thrill were elicited. A diastolic murmur was present from the start. A correct diagnosis was made ante mortem. Death from massive cardiac tamponade was sudden.

The blood pressure was somewhat elevated in both cases, with a history of hypertension in the first.

There was no intimal tear in the first case, and the dissection involved only the portion of the aorta within the pericardial sac.

In the second case there was an intimal rent, and the dissection involved the entire aorta and the common iliac arteries, where the aneurysm emptied itself into the arterial lumen, thus forming the so-called "double-barreled aorta."

The various concepts of the pathogenesis and the pathologic findings and the relation of the intimal tear to the dissection were discussed.

Acknowledgment

My thanks to Dr. Harry J. Isaacs for his permission to publish case 1.

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EDITORIALS

CIVIL DEFENSE

On May 7 and 8, there was held in Washington, D. C., a conference on Civil Defense under the auspices of the Civil Defense Administration with Mr. Millard Caldwell, director of this agency, as moderator. To this meeting were invited representatives of over 300 civilian organizations coming from many walks of life. Representatives of the American College of Physicians, as well as other civilian medical organizations were present.

The purpose of the meeting was to alert us to grave danger of attack; to educate us in the means of preventing disastrous loss of life and property in the event of an attack on this country; and to make us aware of the accomplishment of the careful planning and organization against such an attack.

The keynote of the meeting as expressed by Mr. Caldwell was *there is a defense against atomic bombs.* These means have been devised and set forth by the Civil Defense Administration through the medium of radio, television, cinema, and publications. The latter are particularly informative. Material ranging from the organization of national and state defense groups to detailed instruction on the prevention or care of casualties is available.

The second salient point of these discussions was that well-organized civil defense can provide for a significant reduction in the expected casualty rate in the event of an atomic bomb explosion. It is not often remembered that there was no organized defense against atomic or even high explosive bombs in Japan. With adequate protective measures taken in anticipation of bombing it has been estimated that casualties can be reduced at least by 50 per cent.

The future of this program depends on the willingness of the civilian population to recognize the danger and to protect their lives and property by total mobilization rather than "take to the hills." In this design for living, the medical profession is an integral and fundamental part. Without the complete and unstinted support of medical personnel, this program will not and cannot be effective. The members of the American College of Physicians must do more than their part.

Eugene C. Eppinger

VAGOTOMY IN THE TREATMENT OF PEPTIC ULCER

The recent revival of interest in vagotomy was stimulated largely by the studies of Dragstedt.[1] The favorable clinical results reported by him in 1946 [2] led to a trial in many clinics, and a fairly extensive literature on the

[1] Dragstedt, L. R.: Pathogenesis of gastroduodenal ulcer, Arch. Surg. **44**: 438–451, 1942.
[2] Dragstedt, L. R.: Section of the vagus nerves to the stomach in the treatment of gastroduodenal ulcer, Minnesota Med. **29**: 597–604, 1946.

subject has accumulated. In the earlier studies the number of cases was too small and the period of observation far too short to warrant any definite conclusions. Recently, however, several reports have appeared which are more adequate in these respects and present a clearer picture of the limitations and possibilities of vagotomy.[3, 4, 5, 6, 7]

The clinical use of vagotomy is based on extensive physiological studies, both in animals and man, and the rationale of the procedure is reasonable. Adequate section of the vagi depresses both the motor and secretory functions of the stomach. Muscle tone is reduced, spasm is eliminated, peristaltic activity diminished, dilatation of varying degree occurs, and there is prolonged retention of food or barium in the stomach. After three to four days, a substantial partial recovery from this atony usually begins, and there is a continued slow increase in activity, although the preoperative level had often not been attained during a period of observation of a year and more.

Vagotomy abolishes the psychic stimulus to gastric secretion, both in dogs and man, and apparently blocks the stimulating effects of emotional turmoil and tension of psychoneurotic origin. There is a diminution of the volume of fluid and the amount of acid secreted during digestion. There is also a decrease in volume and acidity of the nocturnal secretion in the fasting stomach, which is particularly striking in patients with duodenal and jejunal ulcer, in whom this acidity is much higher than in normal subjects. There is strong evidence that this is one major factor in the development of duodenal ulcer, since in the absence of food the acid is not normally buffered and neutralized and the intestinal mucosa is inadequately protected from the corrosive action of the gastric juice. Clinical observations have shown an increase in combined acid after vagotomy, suggesting that there is more effective neutralization as well as diminished secretion of acid. Vagotomy also prevents the brisk secretion of acid with which the normal stomach responds to a severe hypoglycemia produced by an injection of insulin. Failure to prevent this response is generally regarded as evidence that some of the vagal fibers have been missed, and it is the most dependable clinical test of the completeness of the operation.

Vagotomy does not abolish the capacity of the stomach to secrete acid in most cases, although achlorhydria is found in some. The presence of food in the stomach (not in the mouth) usually stimulates the secretion of acid, and the response to histamine is usually either normal or only moderately reduced. In many cases, followed for a period of a year or more, acid secretion gradually increases, it may reach preoperative levels, and in

[3] Grimson, K. S., et al.: Vagotomy. Clinical experiences during four years, J. A. M. A. **139**: 508–513, 1949. *Ibid.*: Surgery **27**: 49–61, 1950.

[4] Weinberg, J., et al.: Vagotomy in the treatment of duodenal ulcer. Result in 350 consecutive cases, A. M. A. Arch. Surg. **62**: 161–170, 1951.

[5] Walters, W., Belding, H. H., and Lillie, W. I.: Physiological and clinical studies of vagotomized patients. A study of 331 patients, A. M. A. Arch. Surg. **62**: 183–205, 1951.

[6] Report of Subcommittee on Vagotomy for Peptic Ulcer, Fifty-First Annual Meeting, American Gastroenterological Assn., Atlantic City, N. J., April 29, 1950. Not yet published.

[7] *Ibid.*: Second report, Atlantic City, June 8, 1951. Not yet published.

some the reaction to insulin, negative after the operation, again becomes positive in greater or less degree. No adequate explanation for this has been demonstrated, but it seems quite possible that this may be due to a gradual resumption by the stomach of its primitive autochthonous functions rather than necessarily indicate a regeneration of vagal fibers.

In a brief review it is impracticable to present a detailed analysis of the clinical results reported. An attempt will be made to indicate them in broad outline, and the reader is referred to the original reports for confirmation in detail.

Vagotomy rarely has any place in the treatment of gastric ulcer. The frequency of carcinomatous changes in ulcers supposed to be benign (20 per cent or more) makes a subtotal resection almost imperative as a routine measure, provided it is feasible. Furthermore the results in the few cases in which vagotomy has been used have been poor.[8]

It is generally accepted that any type of operation for duodenal ulcer should be restricted to those cases which prove intractable to "adequate" medical treatment or have serious complications—obstruction, perforation or repeated hemorrhages. Vagotomy without a previous or simultaneous drainage operation on the stomach has been performed in a substantial number of such cases. This is almost invariably followed by prompt and complete relief of the "ulcer" pain, which relief is not dependent upon healing of the ulcer. This may be followed shortly by an increased sense of well being, improvement in appetite and gain in weight. If judged solely by healing of the ulcer, the results must be regarded as fairly satisfactory. Weinberg et al.[4] obtained "the same satisfactory healing of ulcer as in cases in which gastroenterostomy or pyloroplasty was performed concurrently." Dragstedt [8] states: "We have not yet encountered a duodenal ulcer which has failed to heal or has recurred when vagotomy was complete as shown by repeated tests." This has not been the general experience, however. Thus Walters et al.[5] observed two proved failures in 21 cases, and there were 44 failures among 728 cases collected by the Vagotomy Committee of the American Gastroenterological Association (1950 report).[6]

Vagotomy alone has proved unsatisfactory primarily because of the untoward symptoms due to gastric atony and dilatation which are very common sequelae, are often distressing and sometimes serious. According to Moore [9]: "If care is taken in dietary management, the prolongation of hospitalization due to poor emptying of the stomach need constitute only a minor problem." This is not the usual experience, however. Many patients continue to have bloating and distress after eating for weeks or months. In a significant number a subsequent drainage operation on the

[8] Dragstedt, L. R., Camp, E. H., and Fritz, J. M.: Recurrence of gastric ulcer after complete vagotomy, Ann. Surg. **130**: 843–854, 1949.

[9] Moore, F. D., et al.: Resection of the vagus nerves in peptic ulcer. Physiological effects and clinical results with a report of two years' experience, J. A. M. A. **133**: 741–752, 1947.

stomach has been required for relief. For these reasons vagotomy has been practically abandoned as an isolated procedure.

Dragstedt has performed gastroenterostomy with vagotomy in 262 cases of duodenal ulcer with satisfactory results, as already noted. Weinberg et al.[4] also carried out both procedures in 221 cases with satisfactory results with respect to healing of the ulcers.

Although a suitable drainage operation markedly lessens the postoperative distention and discomfort in most cases, it by no means eliminates them. In Walters' experience these symptoms were often troublesome, they greatly increased the amount of postoperative care required and prolonged the average period in the hospital from 12 to 29 days. Since it has not been shown that vagotomy improves the late results or reduces the frequency of stomal ulcers, he has abandoned vagotomy as a routine procedure, preferring a simple subtotal gastric resection when this is feasible.

In cases of stomal ulcer following gastroenterostomy or subtotal resection, a simple vagotomy is followed by healing of the ulcer in most cases if there is no obstruction. Thus in the 250 cases collected by the Vagotomy Committee,[6] excellent results were reported in 83 per cent, and persistent or recurrent ulcer in 9.5 per cent. In stomal ulcers following gastroenterostomy, however, subtotal gastric resection with removal of the ulcer has given better results in the hands of most surgeons, and this now seems to be the operation of choice.

It is impossible at present to reconcile these divergent opinions satisfactorily. The difficulty may be due in part to variations in the completeness with which the fibers are sectioned, the necessity of which is stressed by some surgeons. There is difference of opinion, however, as to whether it is practically possible to secure a strictly complete section with any regularity, and also as to whether this is really necessary. If the insulin test is reliable, and its infallibility is questioned, then the operation must be regarded as incomplete in from 10 to 20 per cent of the cases (Walters). A comparison of the response to insulin with the degree of clinical improvement did not show a very good correlation, and this was found by Walters to be distinctly poor in those cases with persisting or recurring ulceration.

Although satisfactory clinical results have been obtained in cases in which vagotomy was known to be incomplete, something closely approaching a complete resection is probably necessary in most cases. Thus Weinberg et al.[4] reported that in 8 cases reëxplored because of unsatisfactory results following vagotomy, it was found that one trunk had been missed, and after section of this trunk, the patients were completely relieved.

Another factor is the thoroughness of the reëxaminations. Reports by questionnaire are less reliable and often optimistic, as a patient with a persistent ulcer will regard himself as well if he has been relieved of his pain, as is not infrequently the case.

The consensus of opinion at present may be best expressed by a summary of the conclusions reported for the Vagotomy Committee by Dr. Sara Jordan.

based on reports of more than 4000 cases.[7] Subtotal gastric resection, with or without vagotomy and gastroenterostomy with vagotomy are all sound procedures which gave results satisfactory to the patients in more than 90 per cent of the cases. Pyloroplasty with vagotomy has been less satisfactory than gastroenterostomy with vagotomy. Gastric resection, with or without vagotomy, has been somewhat more satisfactory in relieving symptoms and in eliminating ulcer than gastroenterostomy with vagotomy, although the mortality after resection was about twice as great. Resection also gave better results in cases of gastrojejunal ulcer. The inclusion of vagotomy with gastric resection has not improved the results of a simple subtotal resection, which was regarded as the operation of choice.

If these conclusions are upheld by future studies over longer periods of observation, vagotomy will be relegated to a secondary rôle. It should still be valuable in selected cases, however, particularly in jejunal ulcers following an adequate gastric resection and probably in cases in which gastric resection is not feasible for anatomical reasons or in which it entails an undue risk. It is to be hoped that this report will not discourage further studies of the subject.

Although gastric resection now seems to be the most effective measure for the treatment of duodenal ulcer which is intractable to medical management, it can not be regarded as the ultimate ideal of treatment. From the physiological point of view it must be regarded as a makeshift which is justified only by expediency, by the fact that it "works." It must be used until at least equally good results can be offered by some more logical and less mutilating procedure. Vagotomy now appears not to furnish an adequate solution of this problem.

P. W. C.

REVIEWS

Psychosomatic Medicine: Its Principles and Applications. By FRANZ ALEXANDER; with a chapter on "The Functions of the Sexual Apparatus and Their Disturbances" by THERESE BENEDEK. 300 pages; 15 × 22 cm. W. W. Norton & Company, New York. 1950. Price, $4.00.

It is only occasionally that a person working in two specialized branches of medicine can contribute to both and also view present knowledge in its historical perspective. Dr. Alexander presents in one concise volume the development and meaning of psychosomatic medicine, its present status among medical specialists, and points out areas for further study. He draws together the major contributions, from early work on hysterical anorexia to current investigations on many disorders, sorting out general belief from scientific facts.

The book is divided into two parts. In Part One, the general principles are discussed, the meaning of psychosomatic medicine; of bodily changes resulting from emotional response to stimuli; of those neurotic conditions in which the emotional response continues beyond the stimulus and causes chronic bodily changes; the extension of the function of the physician to coördinate physical and mental care of the patient. In Part Two the emotional factors in different diseases are discussed; gastrointestinal and cardiovascular disturbances being very thoroughly covered. Disturbances of the sexual apparatus are summarized and briefly discussed in one chapter by Therese Benedek. Therapeutic considerations of specific diseases are discussed under the various chapters in Part Two. This aspect of the book will be clear enough to practicing psychiatrists, but is not complete enough to serve as a therapeutic guide to less experienced physicians. A final chapter is devoted to therapy, the psychosomatic approach, which requires the teamwork of internist and psychiatrist for best results. Brief reference is made to therapeutic technics of other workers as well as the author's.

The material in this book is presented in a lucid style, using definitions, descriptions from case material, diagrams and specific dynamic patterns to help clarify the concepts presented. There is a very complete bibliography of the subject, and indexes to both subject matter and names mentioned in the text. A background knowledge of anatomy and physiology is helpful, but not necessary to the understanding of the theoretical concepts. This book will be extremely useful to students and practitioners of internal medicine, psychiatry, and related fields, for it brings together in one volume a most valuable discussion of principles and applications of psychosomatic medicine as it is being practiced today.

H. W. N.

Clinical Electrocardiography. By ASHTON GRAYBIEL, Captain, MC, USN, Director of Research, U. S. Naval School of Aviation Medicine, Pensacola, Florida. 198 pages; 18 × 25.5 cm. Thomas Nelson & Sons, New York. 1950, 1951. Price, $5.00.

This is an amplified version of the chapter on "Clinical Electrocardiography" which appears in Nelson's Loose Leaf Medicine. The author uses the hexaxial reference system in many illustrations to show the relationship between the bipolar and unipolar limb leads. At times this method of presentation is helpful.

This volume is "intended to be a practical guide to the use of the electrocardiographic method in medical practice." Attempts to simplify a complex subject are to be commended. However, an understanding of the intricacies and complexities of

electrocardiography should be a sine qua non for assuming the responsibilities of rendering an opinion on an electrocardiogram; and for this purpose this text is not adequate. If its object is to enable the reader to understand the electrocardiographic interpretations of others, and to realize the usefulness and limitations of the electrocardiographic method, then this text is recommended for that purpose.

S. S.

Clinical Unipolar Electrocardiography. By BERNARD S. LIPMAN, A. B., M.D., and EDWARD MASSIE, A.B., M.D., F.A.C.P. 232 pages with 191 figures; 14.5 × 22.5 cm. The Year Book Publishers, Inc., Chicago. 1951. Price, $5.00.

This book is an expansion of the booklet "Unipolar Electrocardiographic Notes" prepared by the authors for the students of Washington University School of Medicine and the staff of the Barnes Hospital. The reception which greeted the booklet was so favorable that Dr. Lipman and Dr. Massie were persuaded to compile this more complete monograph. It is intended primarily for those inexperienced in unipolar technics and interpretations.

As the text is devoted primarily to the "V leads," only those situations in which unipolar tracings are of practical or theoretical significance are included for discussion. Thus the introductory sections cover those electrophysical and physiological principles which are necessary to an intelligent understanding of the subject, and the remainder of the text deals in turn with the electrical position of the heart, ventricular enlargement, bundle branch block, myocardial infarction, ventricular aneurysm, pericarditis, acute cor pulmonale, digitalis, quinidine, potassium and calcium effects, and the juvenile precordial patterns. By the same token the arrhythmias and supraventricular blocks are *not* dealt with.

The text on the whole is well written, concise and clear and occupies only the first 148 pages. The following pages are devoted to an excellent selection of some 90 illustrative tracings from the teaching files at Barnes Hospital, each with an adequately descriptive legend. This comprises a most valuable and satisfactory section of the book. A useful bibliography of over 200 references completes the volume.

This work is not entirely above criticism. The beginner is likely to be confused by an already confusing subject and one of paramount importance—the intrinsicoid deflection; for this important component of the precordial tracing is correctly defined on page 37 and then loosely referred to simply as the R′ wave on pages 93 and 98. Again, though the diagrams are generally helpful, several of them would gain by greater realism: in certain places they give an actually false impression. An example of this may be seen in figure 85 on page 129, where lead V_6 should not but does manifest a late intrinsicoid deflection. One is tempted to ask what grounds exist for the assertion on p. 132 that the ventricles contract *simultaneously* when an ectopic ventricular systole occurs.

Despite its defects, which are minor, this book undoubtedly achieves its authors' purpose. It is a text which can be well recommended to the undergraduate or postgraduate student of modern electrocardiography.

H. J. L. M.

Heart Disease In Pregnancy. By A. MORGAN JONES, M.Sc., M.B., F.R.C.P., Deputy Director of the Department of Cardiology and Lecturer in Clinical Cardiology and in Applied Physiology, University of Manchester. 57 pages; 14 × 22.5 cm. Grune & Stratton, Inc., New York. 1951. Price, $1.50.

This monograph presents concisely and clearly the pertinent facts concerning the heart in pregnancy. Based upon broad experience, the author describes the circula-

tion in pregnancy, the diagnosis and management of organic heart disease during pregnancy, confinement, and the post-partum period.

The style is excellent, the organization is good, and the advice is sound. This small, inexpensive volume contains a wealth of information and is recommended to the clinician and obstetrician who have to deal with these problems.

S. S.

The External Secretion of the Pancreas. By J. Earl Thomas, M.D. 149 pages; 14.5 × 22.5 cm. Charles C Thomas, Publisher, Springfield, Illinois. 1950. Price, $3.50.

This monograph summarizes the basic knowledge concerning the external secretion of the pancreas. It is written for both the clinician and the investigator and should prove valuable to individuals of both categories who are especially concerned with diseases of the pancreas. Subjects covered include the morphology of the pancreas; experimental methods of fistula preparation and properties, functions, stimuli and mechanism of secretion of pancreatic juice.

Present knowledge of trypsinogen and trypsin, chymotrypsinogen and chymotrypsin, peptidases, lipase and amylase is presented. The evidence as to whether adaptive changes of the ratio of enzymes occur is considered and the tentative conclusion is reached that in short periods in the same individual concentrations remain parallel.

The author declines to become involved in the controversy regarding the lipotropic effect of pancreatic juice. The concept of "hydrelatic" and "ecbolic" components of the secretion, and the stimuli for them, such as secretin, pancreozymin and parasympathetic stimuli are presented. The status of pancreozymin is not considered entirely clear.

G. E. G.

BOOKS RECEIVED

Books received during July are acknowledged in the following section. As far as practicable those of special interest will be selected for review later, but it is not possible to discuss all of them.

Arzneitherapie der Herzkrankheiten. By Hans-Jürgen Oettel. 253 pages; 24.5 × 17.5 cm. 1951. Georg Thieme Verlag, Stuttgart; Agents for U. S. A.: Grune & Stratton, Inc., New York. Price, Granzleinen DM 27.–

Clinical Pediatric Urology. By Meredith Campbell, M.S., M.D., F.A.C.S., Professor of Urology, New York University Post-Graduate Medical School, etc.: with a Section on Nephritis and Allied Diseases in Infancy and Childhood by Elvira Goettsch, A.B., M.D., Associate Professor of Pediatrics, University of Southern California School of Medicine, etc., and John D. Lyttle, A.B., M.D., Late Professor of Pediatrics, University of Southern California School of Medicine, etc. 1113 pages; 25.5 × 16.5 cm. 1951. W. B. Saunders Company. Philadelphia. Price, $18.00.

Endoscopy as Related to Diseases of the Bronchus, Esophagus, Stomach, and Peritoneal Cavity. By Edward B. Benedict, A.B., M.D., F.A.C.S., Assistant Clinical Professor of Surgery, Harvard Medical School, etc. 373 pages; 23.5 × 15.5 cm. 1951. The Williams & Wilkins Company, Baltimore. Price, $10.00.

Fainting: Physiological and Psychological Considerations. By George L. Engel, M.D., Associate Professor of Medicine and Psychiatry, The University of Roches-

ter School of Medicine and Dentistry, Rochester, New York. 141 pages; 22.5 × 14.5 cm. 1950. Charles C Thomas, Publisher, Springfield, Illinois. Price, $2.75.

From a Doctor's Heart. By EUGENE F. SNYDER, M.D.; with a Foreword by PAUL DUDLEY WHITE, M.D. 251 pages; 23.5 × 15.5 cm. 1951. The Philosophical Library, New York. Price, $3.75.

Lehrbuch der inneren Medizin. By DR. ERNST LAUDA. 715 pages; 25 × 17.5 cm. 1951. Springer-Verlag, Vienna. Price, $8.40.

Lehrbuch der inneren Medizin. By PROFESSOR DR. KARL FELLINGER. 822 pages; 26 × 18.5 cm. 1951. Urban & Schwarzenberg, Vienna and Innsbruck. Price, DM 38.–

Low-Sodium Diet: A Manual for the Patient. By THURMAN B. RICE, A.M., M.D., Professor of Public Health, Indiana University School of Medicine, Indianapolis, Indiana. 103 pages; 24 × 15.5 cm. 1951. Lea & Febiger, Philadelphia. Price, $2.75.

Modern Practice in Infectious Fevers—in two volumes. Edited by H. STANLEY BANKS, M.A., M.D. (GLAS.), F.R.C.P., D.P.H., Senior Physician, Park Hospital, Hither Green, London, etc. 1054 pages (both volumes); 25 × 17 cm. 1951. Paul B. Hoeber, Inc., Medical Book Department of Harper & Brothers, New York. 1951. Price, $20.00.

The Pharmacologic Principles of Medical Practice: A Textbook on Pharmacology and Therapeutics for Medical Students, Physicians, and the Members of the Professions Allied to Medicine. 2nd Ed. By JOHN C. KRANTZ, JR., Professor of Pharmacology, School of Medicine, University of Maryland, etc., and C. JELLEFF CARR, Associate Professor of Pharmacology, School of Medicine, University of Maryland, etc. 1116 pages; 23.5 × 16 cm. 1951. The Williams & Wilkins Company, Baltimore. Price, $10.00.

COLLEGE NEWS NOTES

Tele-Clinic of the A.C.P. St. Louis Session

The American College of Physicians is pleased to announce that prints of Tele-Clinic Number 3, depicting the highlights of the 32nd Annual Session of the College, at St. Louis, Missouri, April 9–13, 1951, are available for local showing. Tele-Clinic films are a new service to the medical profession by Wyeth Incorporated, of Philadelphia. These sound movies, while they report the highlights of proceedings in general, feature abstracts of selected scientific papers presented before the meeting.

This film opens with the cordial welcome of Dr. Ralph A. Kinsella, General Chairman, to the several thousand members and guests assembled in the Kiel Auditorium. The broad aims of the College are set forth in the President's Address, "The Destiny of the American College of Physicians," by Dr. William S. Middleton, then President. Scenes from the Annual Convocation depict the admission of new Fellows, the awarding of Fellowships, Medals and other awards. Dr. T. Grier Miller, Marshal of the Convocation, and Dr. George Morris Piersol, then Secretary General, present the candidates to President Middleton, the Officers, Regents and Governors of the College for Fellowships in the College. The film shows Dr. Ernest E. Irons receiving a Mastership of the College and Sir John Parkinson, of England, the Convocational Lecturer, receiving an Honorary Fellowship, the second in the history of the College. Dr. Cyrus C. Sturgis, Chairman of the Committee on Fellowships and Awards, presents the candidates for special awards—Dr. Rolla Eugene Dyer for the James D. Bruce Memorial Medal; Dr. George Morris Piersol for the Alfred Stengel Memorial Diploma.

From the broad scope of the program, five representative papers are presented in abstract—"Radiation Injury Following an A-Bomb Explosion," by Lt. Col. C. F. Vorder Bruegge of the Armed Forces Institute of Pathology; "Current Concepts of the Coagulation Mechanism," by Dr. Kenneth M. Brinkhous, Professor of Pathology at the University of North Carolina School of Medicine; "A Biblical Introduction to Geriatric Medicine," by Dr. Louis Krause, Professor of Clinical Medicine at the University of Maryland School of Medicine; "The Prevention of Rheumatic Fever," by Dr. Charles H. Rammelkamp, Jr., Associate Professor of Preventive Medicine, Western Reserve University School of Medicine; "Iron Metabolism and the Therapy of Iron Deficient States," by Dr. Carl V. Moore, Professor of Medicine at the Washington University School of Medicine. The film also shows Sir John Parkinson delivering the Convocational Oration, "The Patient and the Physician." President Middleton's remarks close out the Tele-Clinic Number 3.

Any member of the College desiring to schedule a showing of this film may write to the College Headquarters, 4200 Pine Street, Philadelphia 4, Pa. However, he may receive more immediate service by writing directly to the Wyeth Regional Office which serves his locality (see the list below). Please include with your request for the film the proposed date, hour and place of your meeting, the name of the group or organization which will attend and the probable number of the audience. To show this film 16 mm. sound projector equipment is necessary.

Division No. 1, Mr. V. W. Striegel, 289 Hancock St., Quincy 71, Mass.
(MASS., VT., N. H., R. I., MAINE, N. Y.—with exception of counties shown in Divisions 2 and 9)

Division No. 2, Mr. I. R. Swersky, 81 Spring St., New York 12, N. Y.
(N. J., N. Y.—Kings, Queens, Richmond, Nassau and Suffolk counties only)

Division No. 3, Mr. L. J. Hymel, 8100 McCormick Blvd., Evanston, Ill.
(IND., ILL., KY.—with the exception of Boone, Campbell and Kenton counties —MO.—all counties east of, but not including: Mercer, Saline, Livingston, Benton, Laclede, Douglas, Grundy, Pettis, Carroll, Camden, Wright, Ozark)

Division No. 4, Mr. F. Multaler, 2295 University Ave., St. Paul 4, Minn.
(NEBR., IOWA, WIS., MINN., S. D., N. D., MICH.—only counties of: Gogebic, Houghton, Iron, Marquette, Alger, Schoolcraft, Mackinac, Ontonagon, Keweenaw, Baraga, Dickinson, Delta, Luce, Chippewa)

Division No. 5, Mr. L. B. Hardy, Jr., 210 Walker St., Atlanta 3, Ga.
(FLA., LA., MISS., TENN., ALA., GA., S. C., N. C., ARK.—except Miller County, VA.—except Accomac and Northampton Counties)

Division No. 6, Mr. W. H. Westphal, 142 Howell St., Dallas 2, Tex.
(KANS., OKLA., TEX., ARK.—Miller County only, MO.—all counties west of and including: Mercer, Livingston, Saline, Benton, Laclede, Douglas, Grundy, Carroll, Pettis, Camden, Wright, Ozark)

Division No. 7, Mr. H. D. Pilchard, 1301 Folsom St., San Francisco, Calif.
(ALASKA, MONT., WASH., IDAHO, ORE., UTAH, NEV.—except Clark County, CALIF.—except those listed in Division No. 11, HAWAII)

Division No. 8, Mr. D. O. Wilson, 5101 Lakeside Ave., Cleveland 14, Ohio.
(OHIO, KY.—Counties of Boone, Campbell and Kenton, MICH.—all counties with the exception of: Gogebic, Houghton, Iron, Marquette, Alger, Schoolcraft, Mackinac, Ontonagon, Keweenaw, Baraga, Dickinson, Delta, Luce, Chippewa)

Division No. 9, Mr. A. R. Gallagher, 81 Spring St., New York 12, N. Y.
(CONN., N. Y.—the following counties only: Columbia, Delaware, Dutchess, Greene, New York (Manhattan), Orange, Putnam, Rockland, Sullivan, Ulster, Westchester)

Division No. 10, Mr. G. M. Davenport, Jr., 302 S. Central Ave., Baltimore 2, Md.
(D. C., W. VA., MD., DEL., PA., VA.—counties of Accomac and Northampton)

Division No. 11, Mr. E. V. Scott, 890 E. 62nd St., Los Angeles 1, Calif.
(ARIZ., WYO., N. M., COLO., NEV.—Clark County only, CALIF.—the following counties only: Santa Barbara, Tulare (part), Kern, Inyo, Ventura, Los Angeles, San Bernardino, Orange, Riverside, San Diego, Imperial)

FORTHCOMING ORAL EXAMINATIONS, AMERICAN BOARD OF INTERNAL MEDICINE

San Francisco, October 22, 23, 24, 1951, for candidates living in Washington, Oregon, California, Montana, Arizona, Utah, New Mexico, Colorado, Idaho, Wyoming, and Nevada.

New York City, November 12, 13, 14, 1951, for candidates living in New Hampshire, Vermont, Maine, Massachusetts and New York.

Closing date for acceptance of applications was September 1, 1951.

TWENTY-FOURTH GRADUATE FORTNIGHT, NEW YORK ACADEMY OF MEDICINE

The twenty-fourth Graduate Fortnight of the New York Academy of Medicine will be held in collaboration with the New York Heart Association, October 8–19, 1951. The program of panel discussions, hospital clinics, evening addresses, scientific exhibits and demonstrations will concern "Disorders of the Circulatory System." Sessions will be held at the headquarters of the Academy, 2 East 103rd Street, New York City. Fellows of the Academy will be furnished registration cards without application. For others, a registration card will be sent upon receipt of check for $10, payable to The New York Academy of Medicine.

Dr. William Dock, F.A.C.P., and Dr. Mahlon Ashford, F.A.C.P., are Chairman and Secretary, respectively, of the Fortnight Committee. Dr. Irving S. Wright, F.A.C.P., and Dr. Clarence E. de la Chapelle, F.A.C.P., are Chairmen of the Committee on Hospital Clinics and the Committee on Panel Discussions, respectively. Many Fellows of the American College of Physicians appear on the program.

The University of Minnesota announces a Symposium on Rheumatic Fever to be presented November 29, 30, and December 1, 1951. The Symposium is being given with the sponsorship and financial support of the Minnesota Heart Association. Distinguished medical scientists who have accepted an invitation to participate include: Dr. T. Duckett Jones, New York City; Dr. Ann Kuttner, New York City; Dr. Maclyn McCarty, New York City; Dr. George Murphy, New York City; Dr. Francis Schwentker, Baltimore, Maryland; Dr. Chandler A. Stetsen, Cheyenne, Wyoming; Dr. Charles Remmelkamp, Cleveland, Ohio; and Dr. Lowell Rantz, San Francisco, California. Members of the faculty of the University of Minnesota Medical School and the Mayo Foundation will also participate. All interested physicians, teachers, and investigators are cordially invited to attend. There will be no tuition nor registration fees.

Research Grants and Fellowships to Be Made Available in 1952 by the Life Insurance Medical Research Fund

Applications for 1952 grants in aid of research on cardiovascular problems will be received by the Life Insurance Medical Fund up to November 15, 1951. Support is available for physiological, biochemical, and other basic research which bears on cardiovascular problems, as well as for clinical investigation in this field. Preference is given to fundamental research. It is expected that about $600,000 will be awarded in these grants.

Applications for postdoctoral fellowships for training in research in 1952–53 will also be received by this Fund up to November 1, 1951. Preference will be given to candidates who wish to work in the broad field of cardiovascular function or disease and to candidates who wish to work in institutions other than those in which they have obtained most of their experience. A doctor's degree (M.D. or Ph.D.), or the equivalent is required. The annual stipend varies, as a rule being between $3,000 and $4,000, with larger amounts in special cases. Approximately 15 new postdoctoral fellowships will be available.

New grants and fellowships will become available on July 1, 1952.

A number of predoctoral fellowships for basic training in research will also be awarded. Details are available on request.

Further information and application blanks may be secured from the Scientific Director, Life Insurance Medical Research Fund, 2 East 103d Street, New York 29, New York.

New Army Postgraduate Program Includes Internal Medicine Courses

Two courses in Internal Medicine are included in a new series of short postgraduate courses for armed forces medical officers, according to an announcement from the Office of the Army Surgeon General. The purpose of the new postgraduate courses is fourfold: (1) to assure the maintenance of the highest level of health among Army personnel and to provide efficient care of the sick and wounded in accordance with the highest principles of medical care; (2) to provide medical officers in outlying installations an opportunity to keep abreast of recent medical advances and to

outline recent advances in military medicine; (3) to provide for continued development and improvement of methods and facilities for professional education and training within the Army Medical Service, and (4) to develop qualified teachers and instructors in all phases of professional education and training within the Army Medical Service.

A total of 18 courses in nine medical and one dental specialty fields will be given at five Army hospitals, the Armed Forces Institute of Pathology, Washington, D. C., and the Medical Service Graduate School, Army Medical Center, Washington, D. C., during the last six months of this year. Other courses will be given in the second half of Fiscal Year 1952. (Naval and Air Force medical officers have been invited to attend these courses.)

The two Internal Medicine courses are "Present Trends in Internal Medicine," to be given at Walter Reed Army Hospital, Washington, D. C., October 8–12 (attendance limited to personnel from the 1st, 2nd and 3rd Army Areas and the Military District of Washington), and "Recent Advances in Internal Medicine," to be given at Letterman Army Hospital, San Francisco, Calif., November 5–9 (attendance limited to personnel from the 4th, 5th and 6th Army Areas). Both courses will utilize lectures, conferences, round table discussions and clinics.

Medical Officers on active duty will be given priority in the allotment of spaces. It is contemplated that a few spaces will be available for medical officers not on active duty, civilian physicians from other federal agencies in the vicinity of the hospital and civilian physicians in nearby communities. Applications from medical officers on active duty will be forwarded through channels to the Office of the Surgeon General, Department of the Army, Attention: Personnel Division, Washington 25, D. C.; from Air Force and Naval Medical Officers, through regular channels; from medical officers not on active duty and civilian physicians, through channels to the Commander of the installation offering the course.

Kansas City Southwest Annual Clinical Conference

The twenty-ninth Annual Fall Clinical Conference of the Southwest Clinical Society will be held at Kansas City, Mo., October 1–4, 1951. Dr. H. Marvin Pollard, F.A.C.P., Associate Professor of Medicine at the University of Michigan Medical School, is among the guest speakers. His presentations will be "Modern Therapy for Gastroduodenal Ulcer" and "Cirrhosis of the Liver."

University of Florida Graduate School Course in Hematology

In coöperation with the Florida Medical Association and the Florida State Board of Health, the University of Florida Graduate School gave a postgraduate course in Hematology at Jacksonville, June 21, 22 and 23, 1951. Dr. Charles A. Doan, F.A.C.P., Dean and Professor of Medicine, Ohio State University College of Medicine, Columbus, Ohio, was the chief guest instructor. Eighty-one were registered in the Course, and it was considered one of the most successful ever organized in Florida.

V.A. Hospital, Coatesville, Wants Residents in Neurology and Psychiatry

Several openings are available in the residency training programs in neurology and in psychiatry at the Veterans Administration Hospital, Coatesville, Pa. The programs, organized by the Philadelphia Deans Committee, have been approved by the American Medical Association. Both residencies cover a period of three years or less, depending on the previous experience of an applicant, and are designed to prepare residents for certification in neurology or psychiatry by the American Board

of Psychiatry and Neurology. The programs include rotation through the Veterans Administration Hospital, Coatesville, Pa., Veterans Administration Mental Hygiene Clinic, Philadelphia, Pa., the Philadelphia General Hospital and university and hospital out-patient clinics associated with Philadelphia's five medical schools. Applications should be sent to Vincent T. Lathbury, M.D., Executive Psychiatrist, Philadelphia Deans Committee, 111 North 49th St., Philadelphia 39, Pa.

Immunization Information for International Travel

The latest facts on immunization for travelers going to every section of the world are detailed in a booklet just released by the U. S. Public Health Service. The title of the booklet is "Immunization Information for International Travel." It includes official information on the immunizations required and recommended by each country and the immunizations recommended by the Public Health Service as a precautionary measure for persons traveling abroad. Other items of importance to the traveler include an explanation of the procedure for having inoculations recorded on the International Certificate of Inoculation and Vaccination; a list of Public Health Service facilities where yellow fever inoculations can be obtained; and maps showing the yellow fever endemic areas of the world.

All changes in immunization requirements made after the publication of this booklet will be given in the weekly "Communicable Disease Summary," released by the Public Health Service, under the heading "Quarantine Measures." Travelers can obtain this information from local and State health departments.

The booklet may be purchased from the Superintendent of Documents, Government Printing Office, Washington, D. C., for 20¢ a copy.

Gold-Headed Cane Ceremony

June 5, 1951, marked the fourteenth Ceremony of the Gold-headed Cane at the University of California School of Medicine. The coveted award is made annually to the outstanding senior medical student. He is chosen by his fellow students and by faculty members for having in greatest measure the qualities of "a true physician" and for showing "the greatest interest in the care of his patients during the clinical year." An eminent physician is selected to give an address on the occasion, and he, too, receives a gold-headed cane.

The winner of the honor in 1951 was Charles J. Carman, while John Lewis Linville and George W. Smith received honorable mention. The guest speaker was Dr. Roger Irving Lee, F.A.C.P., prominent Boston physician and Harvard alumnus, who is a former president of the American College of Physicians and of the American Medical Association.

The ceremony was first inaugurated in 1939 by Dr. Wm. J. Kerr, F.A.C.P., Professor of Medicine and Chairman of the Division of Medicine. In his own words, Dr. Kerr "sought a device for bringing the Art of Medicine more forcibly to the attention of students, faculty, and of all those concerned with the care of patients. The Gold-headed Cane provided the inspiration." From this beginning came the ceremony which has grown to be one of the most moving traditions of the University of California School of Medicine.

U. S. Public Health Service Hospitals

Hospitals operated by the U. S. Public Health Service under the name "U. S. Marine Hospital" were redesignated as U. S. Public Health Service Hospitals on July 1, 1951. This change will provide a uniform designation for the 21 hospitals now operated by the Service, and will simplify administrative procedures.

Dr. Rudolph H. Kampmeier, F.A.C.P., Nashville, was recently elected Secretary-Editor of the Tennessee State Medical Association.

Dr. George F. Evans, F.A.C.P., Clarksburg, has been reappointed a member of the West Virginia Medical Licensing Board. Dr. Delivan A. MacGregor, F.A.C.P., Wheeling, was appointed a member of the West Virginia State Board of Health.

Dr. Hyman I. Goldstein (Associate), Camden, N. J., was recently elected a Foreign Corresponding Member of the National French Society of Gastro-enterology at their annual meeting held in Paris. Dr. Goldstein addressed the Section on Internal Medicine of the 2nd International Gerontological Congress which was held in St. Louis, Mo., September 9–14, 1951. Dr. Goldstein's topic was "Peptic Ulcer in the Aged."

Dr. Joseph B. Kirsner, of the Department of Medicine of the University of Chicago, has been advanced to Professor of Medicine at that university.

Dr. LeRoy H. Sloan, F.A.C.P., Chicago, and Dr. Arthur R. Colwell, F.A.C.P., Evanston, were guest speakers recently at the annual meeting of the West Virginia Medical Association. They participated in a panel discussion before a combined session of the Section on Medicine of the West Virginia Medical Association, the West Virginia Diabetes Association and the West Virginia membership of the American College of Physicians.

Dr. Nathaniel Uhr, F.A.C.P., Topeka, Kans., as of September 1, 1951, resigned as Assistant Chief of the Medical Service, Veterans Administration Hospital, at Topeka, and accepted an appointment as full-time internist at the Menninger Clinic.

Dr. Rafael Rodriguez-Molina, F.A.C.P., College Governor for Puerto Rico, addressed a meeting of the Puerto Rico Medical Association in Caguas, P. R., on July 8, 1951, on "Folinic Acid in the Treatment of Sprue and Nutritional Macrocytic Anemia." Dr. Ramon M. Suarez, F.A.C.P., addressed the same meeting on the "Treatment of Headache."

Dr. Robin C. Buerki, F.A.C.P., Vice-President in Charge of Medical Affairs at the University of Pennsylvania, will resign this post on October 1, 1951, to become Executive Director of the Henry Ford Hospital, Detroit, Mich.

Dr. LeRoy H. Briggs, F.A.C.P., San Francisco, Calif., William Watt Kerr Clinical Professor of Medicine at the University of California School of Medicine, was one of the honor guests at a banquet of the school's alumni association on the occasion of Dr. Briggs' retirement from the faculty.

The College of Physicians of Philadelphia recently awarded the Alvarenga Prize for 1951 to Dr. George W. Thorn, F.A.C.P., Hersey Professor of the Theory and Practice of Physic, Harvard Medical School, for his contributions on the rôle of the adrenal cortex in health and disease.

Dr. R. Lee Foster (Associate), Phoenix, was elected Secretary-Treasurer of the recently organized Arizona Radiological Society. Dr. Onie O. Williams (Associate), Phoenix, was elected Vice President of the Arizona Society of Pathologists. These two new societies were organized upon the disbanding of the Arizona Association of Pathologists and Radiologists.

Dr. Francis G. Blake, F.A.C.P., Sterling Professor of Medicine at Yale University School of Medicine, has been appointed Scientific Director, Medical Research and Development Board, Office of the Surgeon General, Department of the Army. Dr. Blake's new position is the most responsible civilian post in medical research in the Army. He will assist in planning and supervising the Army Medical Service research and development program, of which over 200 projects already are under way.

The Veterans Administration has announced the appointment of two Fellows of the American College of Physicians to fill vacancies on the Board of Chief Consultants. They are Dr. Charles L. Brown, Dean of Hahnemann Medical College and Hospital of Philadelphia, and Dr. Charles E. Kossmann, Associate Professor of Medicine at New York University College of Medicine. Dr. Brown was appointed Chief Consultant in Internal Medicine, and Dr. Kossmann received his appointment for cardiology.

1951 Directory, American College of Physicians

A completely revised edition of the Directory of the American College of Physicians is at press and will be ready for distribution later in the autumn. It will be furnished free to Life Members of the College. To other members, the pre-publication price is $4.00. To non-members and institutions, price, $5.00.

1949 Directory and 1950 Supplement—A small number still available at cost of postage and handling, $1.00. Naturally, the membership section does not include the new elections during the past year, but other data and information remains essentially complete and reliable. Send orders to: E. R. Loveland, Executive Secretary, American College of Physicians, 4200 Pine Street, Philadelphia 4, Pa.

OBITUARIES

DR. J. CORWIN MABEY

J. Corwin Mabey, M.D., F.A.C.P., died at his home in Montclair, N. J., on December 17, 1950, of myocardial infarction. This brought to a close a long and busy career beginning as a general practitioner and merging into that of an internist with particular interest shown in the field of diabetes.

Dr. Mabey was born in Montclair, N. J., on April 2, 1873. He received his M.D. in 1905 from Columbia University College of Physicians and Surgeons. His internship was served in Bellevue Hospital, New York, N. Y. Following his internship, Dr. Mabey settled in Montclair, and became connected with Mountainside Hospital in that town. He maintained this connection to the time of his death, at which time he held the position of Emeritus and Consulting Physician. Dr. Mabey spent considerable time studying diabetes with Dr. Elliot P. Joslin, M.A.C.P., in Boston, and organized the Diabetic Clinic in the Mountainside Hospital which he directed for many years. He was also Director of the Division of Diabetes and Metabolic Diseases of the Essex County Hospital for Contagious Diseases, Belleville, and Consulting Physician to Essex County Overbrook Hospital, Cedar Grove, and to the Essex County Sanatorium for Tuberculosis, Verona.

In 1920 Dr. Mabey became a Fellow, and in 1938 a Life Member of the American College of Physicians. He was a Diplomate of the American Board of Internal Medicine and a Fellow of the American Medical Association as well as a member of the New Jersey State Medical Society and the Essex County Medical Society of New Jersey.

HARVEY M. EWING, M.D., F.A.C.P.

DR. LAURRIE DODD SARGENT

Laurrie Dodd Sargent, Ph.G., M.D., F.A.C.P., born in Beallsville, Pa., November 29, 1878, died suddenly on April 6, 1951, shortly after visiting a patient in the Washington (Pa.) Hospital.

Dr. Sargent received his early education in the public schools in Beallsville, his PhG. degree from the Valparaiso University in 1900 and his M.D. from the University of Pittsburgh School of Medicine in 1903. He served his internship at the University of Valparaiso in the Department of Pharmacy. His graduate study included work abroad in England and France.

After practicing in Beallsville from 1903 to 1912 he moved to Washington, Pa., where he lived and practiced until his death. He served as President of the Washington County Medical Society in 1929, was a member of Pennsylvania State Medical Society serving as District Councilor for eleven years and was a Fellow of the American Medical Association. Dr. Sargent was one of the organizers of the Washington County Chapter of the Tuberculosis and Health Association. He served in World War I as Captain in the Medical Corps in 1918–1919 located at Camp Dix, N. J. and at Camp Upton, N. Y. He was a Diplomate of the American Board of Internal Medicine, a member of the National Tuberculosis Association, the Pittsburgh Academy of Medicine and Phi Beta Pi Medical Fraternity.

Dr. Sargent was a very active and loyal member of the American College of Physicians from the time he became a Fellow in 1925. He seldom failed to attend the Regional and the National Meetings and, by reason of genial personality and friendly interest in others, he and Mrs. Sargent became close friends with members from all over the United States. He several times acted as alternate Governor for

Western Pennsylvania. His integrity and unselfishness were such that he exerted an important influence in buiilding up a strong local membership of the College.

Dr. Sargent died as he would have wished. It was while at the Washington Hospital to see a patient that death overtook him, and, although he had not engaged in active practice for two years, his courage and fortitude in the face of declining health would not permit him to give up entirely. Almost to the last moment of his life he was engaged in the profession he loved best and practiced so expertly—the profession of healing.

He had a full and useful life.

CHARLES W. MORTON, M.D., F.A.C.P.,
Governor for Western Pennsylvania

DR. GEORGE M. DECHERD, JR.

Dr. George Michael Decherd, Jr., M.A., M.B., M.D., F.A.C.P., Austin, Texas, died at his home March 5, 1951, of chronic lymphatic leukemia.

He was graduated from the University of Texas with honors with the bachelor of arts and master of arts degrees. In 1930, he was graduated with highest honors from the University of Minnesota School of Medicine. After an internship and residency at the Minneapolis General Hospital, Dr. Decherd did postgraduate work on a fellowship at the University of Illinois, Chicago. He was on the faculty of the University of Texas School of Medicine, Galveston, from 1933 until his death, with the exception of the years 1936 to 1938 when he served as Assistant Professor of Internal Medicine at Louisiana State University School of Medicine, New Orleans. Prior to 1946, Dr. Decherd was Associate Professor of Internal Medicine and Director of the Postgraduate Work at the University of Texas School of Medicine, Galveston. In 1946, Dr. Decherd accepted the position of Director of the Student Health Center at the University of Texas and moved to Austin, but he was continued on the Medical School faculty as Professor of Internal Medicine. He played a key part in planning the new University Health Center building, which was opened shortly before his death. Dr. Decherd was commissioned as an Assistant Surgeon of the United States Public Health Service in 1942. He served as chief of staff of Brackenridge Hospital, Austin, in 1949.

Dr. Decherd was a member of the Texas Medical Association, the American Medical Association, and his county society. He was a Fellow of the American College of Physicians, and he belonged to the American Society for Clinical Investigation, American Federation for Clinical Research, Central Society for Clinical Research, and the Society for Experimental Biology and Medicine. He was also a member of the Texas Academy of Internal Medicine, Texas Club of Internists, and the Texas and American Heart Associations.

Dr. Decherd, whose field of research was experimental and clinical cardiology, was the author of more than eighty scientific articles published in various medical journals. He was listed in "American Men of Science." He held a membership in Alpha Omega Alpha, honorary medical fraternity, Sigma Xi honorary science fraternity; Phi Beta Kappa, honorary scholastic fraternity; Phi Chi, medical fraternity. He was a diplomate of the American Board of Internal Medicine.

Although Dr. Decherd died at an early age he made contributions of lasting value in his field and will long be remembered as an inspiring teacher, an able administrator, and an affable and generous friend by many of his professional colleagues.

D. W. CARTER, JR., M.D., F.A.C.P.,
Governor for Texas

DR. GEORGE DOCK

Dr. George Dock was born in Hopeville, Pa., April 1, 1860, and died of pneumonia at Las Encinas in Pasadena, May 30, 1951. He received his degree of Doctor of Medicine in 1884 at the University of Pennsylvania. In 1895, Dr. Dock received an honorary A.M. degree from Harvard University and in 1904 his own University of Pennsylvania honored him with an Sc.D. degree. In 1936 the University of Southern California conferred the LL.D. degree upon him. At the age of 84 he received the American Medical Association Distinguished Service Medal in recognition of his outstanding work in the field of Internal Medicine and Pathology with a particular citation in regard to his research in hookworm. At the age of 89 he was offered a Mastership in the American College of Physicians but could not accept because he was unable to attend the Convocation.

After receiving his medical education in Philadelphia, he took postgraduate work at the Universities of Leipsic, Berlin, Vienna and at Senckenburg Institute of Frankfort, Germany. He then returned to the Hospital of the University of Pennsylvania and was in charge of the Clinical Laboratory from 1887 to 1888 under Drs. William Osler and John H. Musser. Dr. Osler referred to Dr. George Dock as "a man who knows more about clinical laboratory procedures than anyone in the United States." Thus began a career of teaching and investigation which was to carry Dr. Dock to professorships in four great medical schools in the United States—the University of Texas from 1888 to 1891, the University of Michigan from 1891 to 1908, Tulane from 1908–1910 and Washington University from 1910 to 1922. It was a day of great fortune for Southern California when, in 1922, Dr. Dock decided to make his home in Altadena, California.

Dr. Dock played a great part in creating the modern age of medicine. In 1896 he published the first account of a case of coronary thrombosis in America, diagnosed during life and confirmed by autopsy findings. Written in association with Dr. C. C. Bass, of New Orleans, Dr. Dock's book, "Hookworm Disease," was a great influence in helping eradicate this evil. He was a master of clinical recognition of disease through physical examination and close observation but urged the use of every diagnostic aid, and throughout his life sought verification of the clinical diagnosis by postmortem examinations. After coming to Southern California in 1922, he became actively interested in advancing medicine in this area. With the revival of the medical school at the University of Southern California, Dr. Dock became a member of its Board of Trustees and an Honorary Professor of Medicine. He gave over 1,500 valuable volumes to the Los Angeles County Medical Library. Eleven years ago this Association established the George Dock Lectureship in the History of Medicine. A bibliography of the writings of Dr. Dock is 158 separate articles extending from the year 1888 to 1949.

He was a member of Chi Phi, Nu Sigma Nu, Sigma Xi, and Alpha Omega Alpha fraternities. His affiliations were many, including the American Society of Tropical Medicine, National Tuberculosis Association, Central Interurban Clinical Club, and Pacific Interurban Clinical Club; President, 1916–17, Association of American Physicians; Diplomate, American Board of Internal Medicine; Fellow (1924), American College of Physicians.

Dr. Dock was the proud possessor of a replica of the famous "Gold-Headed Cane" carried by Dr. John Radcliffe, the great British physician. This replica was presented to him by the University of California in 1943. The original is preserved by the Royal College of Physicians in London.

Dr. Dock is survived by his widow, Miriam Gould Dock and two sons, George Dock, Jr., and Dr. William Dock, both of New York. William Dock is the Professor

of Medicine at the State University of New York College of Medicine in Brooklyn. A son of George, Jr., Donald S. Dock, is now studying Medicine at Johns Hopkins University School of Medicine.

LELAND HAWKINS, M.D., F.A.C.P.,
Governor for Southern California

DR. LESTER JAMES WILLIAMS

Dr. Lester James Williams was born in Opelousas, Louisiana, November 19, 1880; he died at Our Lady of the Lake Hospital on March 15, 1951, of coronary thrombosis.

Dr. Williams graduated from Louisiana State University with a B.A. degree in 1900, and from Tulane University of Louisiana School of Medicine in 1904. He interned at the Lagaretto Hospital for Yellow Fever, located at the mouth of the Mississippi River.

He then practiced medicine in Melville, Louisiana, from 1908 to 1917 whereupon he entered the Medical Corps of the U. S. Army, serving through World War I, and advancing to the rank of Lieutenant Colonel. He had specialized in Radiology and after his discharge from the Army he followed this specialty in Baton Rouge, Louisiana, up to the time of his death.

Dr. Williams was a member of the Louisiana Hospital Board Service, a past President of the East Baton Rouge Medical Society, a past President of the Louisiana State Medical Society, a Life Fellow of the American College of Radiology, a member of the British Institute of Radiology, served on the Board of the Baton Rouge General Hospital and on the staff of Our Lady of the Lake Hospital. He had been a Fellow of the American College of Physicians since 1928, a Life Member since 1941.

DR. CAROLINE KREISS PRATT

Dr. Caroline Kreiss Pratt, R.N., A.B., M.D., Atlanta, Ga., was born in San Mateo County, Calif., July 22, 1915, received her A.B. from the University of California, 1938, and her M.D. from Washington University School of Medicine, St. Louis, 1942. She interned at the University of California Hospital, San Francisco.

At the time of her death, Dr. Pratt was Medical Officer in Charge of Medical and Dental Services at the Communicable Disease Center, Chamblee, Ga. She was also Assistant in Medicine at Emory University School of Medicine and a member of the Visiting Staffs of the Grady Memorial and Crawford W. Long Memorial Hospitals. Previously she had been Medical Director of the Atlanta Regional Red Cross Blood Center.

Dr. Pratt was accidentally drowned on May 22, 1951, at Fernandina, Fla., while attempting to rescue her young son who had wandered into deep water. Her husband effected the son's rescue. All attempts to revive Dr. Pratt were without success.

The death of Dr. Pratt has been a distinct loss to our community, as she was a most enthusiastic, industrious and capable physician and had done much for the advancement of better medicine in this community. She was constant in her attendance at the A.C.P. meetings, and she will be greatly missed by the Fellows and Associates of this State. She became an Associate of the College in 1946.

CARTER SMITH, M.D., F.A.C.P.,
Governor for Georgia

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